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Plasmapheresis in obstetrics and neonatology

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The book provides pathogenetic substantiation of apheresis therapy and indications to it in various types of obstetrics and neonatology complications. There are shown advantages of membrane plasmapheresis.

The book is intended for both, specialists in apheresis therapy, resustitation and obstetricians and newborn doctors.
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INTRODUCTION

Human health is established even in the period of its prenatal development. Many researchers in their studies indicate an association of various diseases in children, especially such as allergies (including atopic dermatitis, bronchial asthma), chronic bronchitis, kidney disease, with disorders of pregnancy of their mothers. In obstetrics is important not only to ensure optimal conditions and the security of the delivery, but also to create favorable conditions for the development of the fetus throughout pregnancy. Despite all the achievements of modern health care, there is still a high enough level of threatened abortion and preterm birth, perinatal morbidity and mortality. And all this was the basis for study of the causes and pathogenesis of the major complications of pregnancy, the development of measures of prevention and treatment.
Preeclampsia

Preeclampsia is a serious complication of pregnancy, one of the leading causes of maternal and perinatal morbidity and mortality. In most cases it is secondary or combined nature, developing on the background of other types of extragenital pathology – diseases of the kidney (pyelonephritis, glomerulonephritis), obesity, hypertension, diabetes.

Old version of this complication – toxemia of pregnancy – more fully reflect the essence of this pathology. However, among the many hypotheses about the etiology and pathogenesis of preeclampsia is prevalent view of the leading role of generalized spasm of peripheral vessels with impaired microcirculation. And supposedly due to spasm of the arterioles increases vascular permeability and transition fluid in tissues and hypovolemia.

Of course, we must accept the presence of such processes, but they are developing, in all probability, in reverse order, that is, really is a violation of vascular permeability, but not as a result of spasm of blood vessels, and due to the accumulation in the blood of some toxic membranotropic substances. But at the same time developing a toxic edema interstitial with transition there also proteins, primarily albumin, and certainly accompanied by hypoproteinemia. The latter, as a result of reducing the colloid osmotic pressure of blood plasma, which inevitably leads to a decrease in circulating blood volume, and an adaptive response as when it occurs arteriolar spasms to reduce the volume of the vascular bed and the blood pressure necessary to maintain.

Therefore, we must first of all interested in those changes in the body that determine the development of endogenous intoxication syndrome. There are reports of significant violations of biochemical homeostasis in preeclampsia, in particular - disorders of the kallikrein-kinin system, lipid peroxidation, proteolysis with the accumulation of a number of toxic metabolites and BAS - kinins, histamine, serotonin, malondialdehyde, diene conjugates, medium weight oligopeptides. Thus, according to V.V. Vetrov (1990, 2000), the levels of “middle molecules” in normal pregnant and preeclampsia I, II and III degrees up 247.0 ± 7.2, 282.8 ± 8.4; 363.2 ± 6.7 end 534.2 ± 13.5 units respectively, and in some cases (eclampsia anuric) reach 1000 units.

May play a role, and endotoxin (bacterial lipopolysaccharide) are released into the bloodstream when "irritable bowel syndrome" for violations of its motor-evacuation function and flatulence. In such cases, 86% of pregnant women registered threatened miscarriage [Demina TN, Suhurova LS, 2008].
These products also are capable of increasing the permeability of the vascular endothelium with access to the interstitium not only fluid, but also protein, thereby causing hypovolemia and generalized vasospasm respectively.

In women with the metabolic syndrome, obesity and gestational diabetes preeclampsia develops much more and is accompanied by asphyxia and neonatal cerebral blood flow disorders [Nikolaeva-Ball D.R. et al, 2008].

Not ruled out an autoimmune component of preeclampsia when autoantibodies activate angiotensin receptors that confirm special studies in animal experiments [Xia Y., Kellems R.E., 2009]

Preeclampsia is accompanied by a systemic inflammatory response syndrome with the release of cytokines IL-6 and TNF-α and disorder of lipid peroxidation with depletion of the antioxidant defense capacity. Toxic damage of hepatocytes promotes additional release of C-reactive protein [Medvinsky I.D. et al, 2000].

The role of a vascular endothelial growth factor (VEGF), placental growth factor (PIGF) and soluble fms-like tyrosine-kinase receptor-1 which detection is possible even before emergence of clinical signs of a preeclampsia is revealed [Andraweera P.H Proslezhitvatsya. et al., 2012] which removal from maternal circulation can help to prevent development of a preeclampsia [Alasztics B. et al., 2014].

The result is interstitial edema and hypoxia organs and tissues with secondary deterioration of their functions. In severe cases of eclampsia occurs on a background of multiple organ failure – loss of consciousness, seizures (brain edema), severe parenchymal respiratory failure (toxic pulmonary edema – respiratory distress syndrome [RDS]), anuria, liver failure, hypertension with impaired microcirculation, and often with retinal detachment.

Development of multiple organ disorders contributes to a series of vicious circles, among which the leading role belongs nephropathy, when due to the toxic effects begin to suffer the main elements of the nephron – glomerular filtration and tubular reabsorption. This process results in a progressive increase in the concentration of toxic substances of middle weight that normal kidney safely brought to the urine. And it takes away some researchers nephropathy leading role in exacerbating the disorders of homeostasis and progression of preeclampsia [Vetrov V.V., 2000].

Membranotropic biologically active substances (BAS) affect not only the vascular endothelium, but also in other cell membrane structures, disrupting transmembrane exchange of electrolytes and other substances. No exception, and the cells of the blood itself, taking the first blow of toxic compounds. In particular, the membranotropic products stimulate platelet aggregation, thereby contributing, development of disseminating intravascular coagulation (DIC), platelet aggregation and thrombocytopenia, increased concentration of fibrin degradation products, soluble fibrin monomer complexes and reduced fibrinolysin activity [Chaika V.K. et al, 2004]. And it
develops consumption of coagulopathy, which is the cause of severe bleeding during delivery.

In preeclampsia can be traced and immune mechanisms of conflict between mother and fetus also. There is revealed part of fetal antibodies and autoantibodies in the pathogenesis of preeclampsia. Can not exclude the role of local immunity to immune damage the placenta and increase the activity of natural killer cells, deposition of the circulating immune complexes (CIC) in the vessels of the placenta and kidney, kinins activation, increased levels of thromboxane, fibrin deposition. This leads to ischemia of the placenta and kidney development of hypertension. Antibodies and CIC seating on platelets, activate their adhesiveness to the release of ADP and serotonin, which triggers a cascade of DIC.

Special electrophysiological studies show that at the earliest clinical manifestations of preeclampsia there can already detect signs of placental circulation disturbances and intrauterine hypoxia. This is understandable, since all middle weight toxic products freely cross the placental barrier, which was confirmed by our own research – the level of middle molecules in the blood of pregnant women with symptoms of preeclampsia are completely consistent with their concentration in placental blood, i.e., in the fetal blood.

This shows that all membranotoxic products that cause deteriorations of endothelial permeability, edema, and toxic disorders of the organs of pregnant, just break and placental circulation also, with degenerative processes in the placenta with sclerosis, necrosis, hemorrhage and its partial detachment that is driving force for premature labor and severe bleeding. Thus both the maternal and cord blood and even in the amniotic fluid increases the content of IL-8 and TNF-α. Violations of placental circulation also determine gas exchange disorders and fetal hypoxia, delay its development the fetus retardation [Radzinsky V.E. et al., 1999].

It endotoxemia, causing impaired permeability of the vascular wall and leads to the development of interstitial edema is actually toxic, promotes fluid retention pregnant. The appearance of protein in the urine also suggests increasing the toxic permeability of renal vessels. Nevertheless, O.V. Grischenko et al. (2008) is the increase in extracellular fluid volume during pregnancy, reaching 4,4-5 liters and accompanied by edema of the lower extremities, deem appropriate physiological pregnancy. However, it is difficult to imagine that such fluid accumulation volume is a normal condition.

Prolonged fetal conditions such toxemia breaks all processes of development of fetal organs and systems, up to his death in utero. The intrauterine fetal growth retardation syndrome is one of the leading places in the structure of perinatal morbidity and mortality. Its frequency varies from 3 to 24% of mature and from 18 to 24% of premature babies. In children with intrauterine fetal growth retardation and
perinatal mortality and morbidity is 2-3 times higher than those in children with normal body weight and reaches 80-100% [Likhacheva N.V., 2000].

There is the most actual problem of neurological disorders in preterm. In particular, the incidence of severe neurological disorders they can reach 44-47% [Savelieva G.M. et al., 1999; Crane J.M. et al., 2015]. Thus, among neonates with birth weight below 1000g most of die in the first hours and days of life, and in survivors severe disabling CNS disorders reach 28%, and less rough - 44%. Of the 100 such children born healthy are only 8-15% [Kulakov V.I. et al, 1998].

These children in the future will suffer encephalopathy with mental retardation, pneumopathies with respiratory distress syndrome, hepato-nephropathy with the formation of chronic hepatitis and even early cirrhosis, chronic pyelonephritis, will lag behind in physical development. The incidence of lung disease in children whose mothers suffered preeclampsia during pregnancy is twice that of the children born in normal pregnancy [Mahon B.E. et al., 2007]. Allergic dermatitis (atopic eczema) in such cases also occur 3-4 times more likely [Evsyukova I.I., 2001]. Increases the risk of perinatal and neonatal sensitization, reaching 31.8%, and at increased load pregnant drugs it comes to 66.6% [Gavalov SM, 2001].

V.K.Chayka and T.N.Demina (2003) rightly point out that as a bookmark main organs and systems, and, ultimately, human health is largely dependent on the conditions of fetal development and the factors of the environment, which in affect it. A fetal external environment is the internal environment of the body of his mother.

Pregnancy - is a physiological state of immunodeficiency, which allows to block the struggle against foreign antigens of the fetus to the mother, who is actually a "transplant". However, disturbances of biochemical homeostasis in preeclampsia cause additional secondary immunodeficiency toxic origin. The same processes occur in the fetus, the immune system is still evolving, but under prolonged exposure to toxic products of the immune system development even more inhibited and the child is born in such cases as completely defenseless before microorganisms (there are increased the frequency of septic complications, respiratory viral diseases) and the xenobiotics (frequent allergies – diathesis, asthmatic bronchitis), and before the tumor cells (rejuvenation of cancer). Virtually it holds the acquired immunodeficiency syndrome, like AIDS actually, with all its fatal consequences.

Preeclampsia or toxemia of pregnancy – it can be said the only disease in the name includes the term "toxicosis", but a statement of this fact is far means that detoxification is the main therapeutic measure. Instead measures targeted removal of pathological products from the body of a pregnant, she is assigned a number of different drugs, often far from indifferent to the fetus. Many of them, each in their own way, seem to be quite justified – euphylin, komplamin, nikoshpan, curantyl, trental, heparin, glucose, potassium orotate, glutamic acid, methionine, tocopherol, essentiale, vitamins and many other [Bychkov V.I. et al., 1999; Strizhakov A.N. et al., 2000].
On the other hand, it is obvious that instead of introducing any additional substances should, on the contrary, remove pathological products and best this can be accomplished only by means of the apheresis therapy.

One of the first V.V.Vetrov with detoxification in preeclampsia has used hemosorption. However, despite the positive results obtained by cupping manifestations of preeclampsia, prolongation of pregnancy and the birth of healthy babies and live (Vetrov V.V., Levanovich V.V., 1990), this method at the time did not get due recognition and distribution in obstetric practice.

Understanding the rationale for such a cautious stance obstetricians on the one hand and the need for detoxification therapy in preeclampsia, on the other hand, we decided to use at first the safest and non-invasive method of detoxification – enterosorption using polyphosphate. Given that observed during pregnancy disorder known enzymatic and motor functions of the intestine with impaired processes of digestion, dysbiosis, which leads to the appearance of enterogenous toxins (endotoxin) that getting into the bloodstream exacerbate toxicosis, this alone is an indication for enterosorption.

However, at the level of the intestinal villi is a constant process of fluid flow from the vascular bed (5-10 liters per day) consisting of all components of plasma except proteins. As a major toxic metabolites in preeclampsia are of middlemolecular weight, then they have the ability to temporarily leave the bloodstream and enter the intestinal lumen. If they are there to meet with the activated surface enterosorbent, thanks to its electrochemical properties (most of their molecules contain free radicals) are adsorbed on them and never returned to the circulation during the reverse fluid reabsorption in the intestine [Enterosorption, 1991].

Method in the treatment of pre-eclampsia enterosorption was used by us in the course of medical and environmental research in the Voljsky city (near Volgograd) were identified both a higher perinatal mortality on the background of complicated pregnancy and a greater children incidences. Indications for enterosorption served as early toxicosis and manifestations of late toxicosis at all stages of pregnancy. Treatment was performed as an outpatient under the supervision of physicians antenatal clinics, and in the Department of Pathology of pregnancy hospital. The course consisted of receiving polyphosphate 1 tablespoon three times a day on an empty stomach for 7-10 days. If necessary, these courses were repeated at intervals of not less than 1 month, up to the period immediately preceding the delivery.

Effectiveness of such apheresis therapy was most prominently in the early toxicosis when vomiting stopped 2-3 days after starting treatment. When late toxicosis (preeclampsia) also noted smoothing their manifestations – normalized blood pressure, reduce edemas, disappeared or decreased levels of protein in the urine, decreased degree of intrauterine fetal hypoxia, starred threat of premature birth. Any
complications and side effects associated with enterosorption not mentioned [Voinov V.A. et al., 1994].

There is leaded a more detailed analysis of 780 stories of childbirth and newborn status with the release of the two groups. 1st group consisted of 183 children whose mothers took during pregnancy polyphepane, 2nd – 597 children whose mothers did not take it.

This analysis showed that the perinatal mortality rate as a whole was 10.2‰ (8 from 780), but in the 1st group of children whose mothers took Polyphepanum, died only one newborn (of twins) weighing 1110 g, which was 5.4‰, against 11.7‰ (p<0.01) in the 2nd group of children whose mothers did not take polyphepane. It should be borne in mind that in this city over the previous years levels of perinatal mortality were 16.2‰ and 19.4‰, and among the residents of the Voljsky, who gave birth in the regional hospital, where the enterosorption method was not implemented (as in the guide a women's clinic in the city), perinatal mortality rate for the corresponding period in 1993 amounted to 21.7‰ (10 neonates from 460).

There was identified and a clear tendency to reduce the frequency of pulmonary complications (from which mainly depends early neonatal mortality) in the group of children whose mothers took during pregnancy polyphepane. In addition, there observed lower incidence of neurological complications in this subgroup of infants.

Indirect indicator of the health of newborns is the possibility of discharge home with his mother, or, otherwise, the need to relocation for further treatment in the department of pathology of the newborn, or even more intensive therapy in the intensive care baby unit. Analysis of these cases showed that the need for relocation of newborns whose mothers took polyphepane as a children's hospital and in the ICU, there is even less likely than in the control group (1.1 and 3.3%, respectively), while it is in this subgroup of children such a need would have to occur much more often due to complications of pregnancy in their mothers. This, albeit indirectly indicates a higher level of health of newborns whose mothers took preventive detoxification courses in various forms of toxicosis pregnant and comorbidity. This confirms the fact that among the 16 children analyzed group died from various causes during the first year of life, there was not a single child whose mothers took polyphepane.

Thus, these data show that in the absence of any negative side effects, even a mild preventive detoxification using polyphepane largely prevents the development of a number of serious complications in newborns. However, we are aware of and that is not in all cases, such therapy is sufficient in relieving severe manifestations of preeclampsia. Later we used and a much more efficient method of apheresis therapy as plasmapheresis.

In the D.O. Ott Institute of Obstetrics and Gynecology name (St. Petersburg) in early preeclampsia, characterized by repeated vomiting with weight loss and acetonuria courses membrane plasmapheresis led to a significant improvement in the
general condition. Stopped nausea and vomiting, appetite appeared, restored body weight, decreased by 77% the level of middle weight molecules. All women managed to carry a pregnancy. Additional justification for such an active approach to therapy of early toxicity are evidence that in violation of the uteroplacental circulation in the I trimester up to 88.5 % of pregnant women subsequently develop preeclampsia [O.B. Panina, 2000; Chortatos A. et al., 2015].

In the Snegirev maternity hospital (St. Petersburg) in 123 pregnant women with preeclampsia was also used membrane plasmapheresis. 3-5 sessions performed with the removal of up to 30% circulating plasma volume (CPV) at intervals of 2-3 days. The compensation is carried isovolemic mode only crystalloid solutions. After plasmapheresis pregnant noted improvement in health, stopped headaches, decreased edema, increased urine output, decreased by 20% the level of hypertension. Normalized transaminase (ALT) and bilirubin levels, decreased plasma coagulation factors, although remained elevated adhesive-platelet aggregation properties, but in any case not observed bleeding during delivery. Stable clinical effect was observed in 39 pregnant women with preeclampsia mild. All of them gave birth in time and sent home with the children. In a group of 84 pregnant women with severe preeclampsia clinical effect was less resistant – 60% of women were discharged home ahead of schedule and 40% of newborn body weight at birth was until 1500, however, perinatal loss had no children. All of them recovered and were discharged after treatment and rehabilitation in children's hospitals in the city.

When comparing comparable groups of women with pre-eclampsia has been shown that the use of apheresis therapy has reduced the incidence of intrauterine infections, prematurity, hypoxia and fetal malnutrition in 2.6, 1.6, 1.5 and 1.3 times respectively. In this case, the control group (49 women) died perinatally 2 fetal from intrauterine infection and hypoxia, whereas in the study group (46 women), perinatal mortality was not [Vetrov V.V., 2000]. At severe depression of liver function apheresis therapy started with hemosorption and followed by membrane plasmapheresis. Over 10 years have been on the treatment of 1049 pregnant women with preeclampsia in the absence of perinatal mortality in this group [Vetrov V.V. et al., 2009; Serov V.N. et al., 2011].

Using plasmapheresis it helps normalize blood clotting, preventing bleeding and reduce the risk of thromboembolic complications [Chaika V.K. et al., 2004]. And there was the normalization of the main markers of intoxication – medium weight oligopeptides and leukocyte index of intoxication [Chermnykh S.V., 2006]. Even in preterm labor outcomes of gestation in women treated for pregnancy by apheresis therapy were the best. If the control group 70% of the infants required relocation to the intensive care unit at Children's Hospital, the main group of such a need arose in 2 times less [Vetrov V.V. et al., 2003]. Best results are obtained when plasmapheresis was combined with ozone therapy [Chermnykh S.V. et al., 2006].
A great experience with plasmapheresis in obstetrics and in the treatment of preeclampsia, in particular, gained in the Scientific Center for Obstetrics, Gynecology and Perinatology, Moscow [Kulakov V.I., 1998; Serov V.N., Fedorova T.A., 2003, Serov V.N. et al., 2011]. As a result of plasmapheresis noted distinct decrease in proteinuria and improvement of renal function with an increase in glomerular filtration rate, diuresis and clearance minute indicators. There were improved performance both fetoplacental circulation and fetal status according to CTG, normalized system of lipid peroxidation with decreased blood concentrations of toxic products of lipid peroxidation. It was noted faster regression of edema syndrome, reducing the frequency of septic complications from 70% to 16%, lactation persisted in 53% (vs. 30% for conventional therapy), 2.7 times decreased maternal mortality, decreased puerperal stay in the maternity hospital in 1.5 times [Pyregov A.V., 2005].

In Ukraine, the largest (20-year) experience of apheresis therapy in obstetric practice accumulated in the Donetsk regional center of maternity and childhood [Chaika V.K. et al., 2009]. Timely inclusion membrane plasmapheresis in complex intensive treatment of severe preeclampsia allowed to reduce manifestations of endogenous intoxication prolong pregnancy up to 48 hours, followed by delivery to prevent maternal mortality and multiple organ dysfunction stabilized level on stage, did not require replacement therapy [Demina T.N. et al., 2009].

The plasma exchange finds application and in Germany as "rescue therapy" at refractory forms of a preeclampsia [Müller-Deile J., Schiffer M., 2014].

"Hidden" urogenital infections syndrome

Fetal development threatens another danger – in the presence of intrauterine infection in pregnant “hidden” urogenital infections syndrome – chlamydia, mycoplasma, ureaplasma, toxoplasmosis, bacterial vaginosis, cytomegalova- and herpes viruses. During the life of women before pregnancy, these infections may not cause significant disturbances occur and periodic exacerbations cystitis, adnexitis, vaginitis. However, during pregnancy the main danger threatens the fetus, causing defects and violations of its development up to the termination of pregnancy in the early stages (i.e., actually infertility), premature birth, and even fetal death. However, the born alive child has signs of intrauterine and postnatal infections (45%), morphological and functional immaturity and intrauterine growth retardation (18%), serious depression of the functions of the brain (23%), liver, kidneys, lungs [Bocharova I.I. et al., 2001].

V.K.Chayka and T.N.Demina (2003) emphasized that almost no patients with miscarriage, which would not have been the persistence of several viruses or combinations thereof, with intracellular protozoal infections. On the other hand, I.B.Goda et al. (2005) showed inflammatory changes of placentas in 100% of patients
and infections in 80% of stillborn fetuses, allowing the infectious factor considered the
main cause of spontaneous abortion and stillbirth in terms of 22-27 weeks.

Consequences of these infections and conditions are placentitis with hyalinosis
and focal necrosis, and amnionitis with impaired uteroplacental circulation and fetal
hypoxia. Exacerbation of pyelonephritis causes concomitant development of
preeclampsia, which further exacerbates the adverse conditions for the fetal
development.

The most common intrauterine infection is cytomegalovirus (CMV or herpes
virus 5). In the USA it is the main reason of a delay of pre-natal development of a fetus
and its various defects, including neurologic complications, hearing and vision loss
[Tabata T. et al., 2015]. CMV antibodies can be detected in 45-100 % of the population
[Festary A. et al., 2015]. At the same time after the initial infection obligate formed
lifelong persistence of CMV in the body. Immunodeficiency, including physiological
immunosuppression during pregnancy, promote activation of CMV infection.
Furthermore, the infection itself can promote immunosuppression. The frequency of
intrauterine infection reaches 70%, the risk of transmission of CMV to the fetus is 40-
50%. When fetus was infected in the early stages of its development they can occur
deformities and even death of the fetus or newborn. However, most infants with
congenital infection, there are no symptoms, however, in the future they may be
suffering from multiple complications, including atrophy of the optic nerve and
sensorineural deafness and mental retardation, and even cerebral palsy [Chaika V.K.
et al., 2004].

Almost all women have anemia during pregnancy, CMV infection is more
pronounced anemia. While there is an increase in the degree of aggregation of red
blood cells deteriorate gemoglobin synthesis processes can violate the structure and
function of erythrocyte membranes. Accelerated aging of red blood cells and develop
the quality of their inferiority.

Virtually all women were those or other pregnancy complications. At 48.1%
diagnosed threatened miscarriage, at 7.6% of installed non-developing pregnancy with
gestational ages of 9 and 12 weeks, 24% of spontaneous abortions occurred in terms
of 14-27 weeks, 70.9 % identified pathology of amniotic fluid, in 46.8% identified a
syndrome of intrauterine growth retardation. In 44.4% of cases occurred preterm labor
and normal delivery occurred in only 5.5% of women with cytomegalovirus infection.
Perinatal losses occurred in 26.6% of women and 50% of healthy children at birth in
the future are identified deafness and impaired mental and physical development
[Chaika V.K. et al., 2005]. High risk of micro- or hydrocephalus, cerebral palsy, delayed
mental and psychomotor development, chorioretinitis and optic atrophy with loss of
vision until blindness [Mardanli S.G. et al., 2005]. In many cases, neurological
symptoms not seen neonatologists, however on closer examination can detect
decreased muscle tone at the phenomena of hyperkinetic facial muscles with prolonged retention of hyperkinetic syndrome [Maximchuk L.V., 2006].

No less danger is **genital herpes** or herpes simplex virus type 2 (HSV), which affects up to 30 million adults in the United States, and the incidence of infection in Moscow it is 19.7%. It is transmitted through sexual contact. When genital herpes there are detected decrease in the total number of CD3+ and CD4+ cells, inhibition of the activity of natural killer cells and the ability of lymphocytes to the synthesis of endogenous interferon, reducing the total number of leukocytes and monocytes [Mirzoyan J.V., 2000]. Genital herpes can lead to tubes obstruction and infertility. When intrauterine infection of the fetus delayed its development with the emergence of micro- and hydrocephalus and intrauterine pneumonia. In the first half of pregnancy increases the risk of spontaneous abortion, and then – premature birth. HSV infection in 30-50% of cases determines the frequency of spontaneous abortion, non-developing ("stilled") pregnancy, premature birth, perinatal morbidity and mortality [Chaika V.K., Shemyakina N.N., 2004; Lopez-Medina E. et al., 2015]. Herpes hepatitis is more common during pregnancy, with a neonatal risk at peripartum period [Dochez V, Ducarme G, 2015]. Cases of herpetic damage of a liver at pregnancy with development of an acute liver failure for which knocking over the plasma exchange was used are described [Holt E.W. et al., 2013].

In addition, chronic HSV infection promotes activation of autoimmune processes, in particular antiphospholipid syndrome (APS), which occurs in 20-51% of these patients. In the milder cases of APS frequency up to 10% of cases, and in severe herpes infection reaches 64.7% [Linnikov V.I., 2004], which largely determines the frequency of miscarriage. The reasons for such activation of autoimmune processes are not entirely clear. Maybe they explained increased release of cytokines in areas of active inflammation caused by HSV infection. In particular proved the role of interleukin 10 (IL-10) in the overstimulation of B-lymphocytes with generation alloimmune antiphospholipid antibodies. In addition, we can not exclude the phenomenon of molecular mimicry due to the proximity structure of virus antigens and antigens of the host. In recent years, information about the role of vaccine herpes infection in overstimulation of antibody, the consequence of which is the development of autoimmune processes, activated of such proximity HSV and human antigens [Chaika V.K., Demina T.N., 2004].

**Epstein-Barr virus** (EBV) also applies to herpes (herpes virus 4), and is no less dangerous, predisposing to premature termination of pregnancy, fetal malnutrition, while births causes damage to the nervous system (28%), eyes (7 %), recurrent chroniosepsis (13%), hepatopathy and respiratory distress syndrome [Chaika V.K., Demina T.N., 2003]. High probability of intrauterine infection of the fetus, which in later life may be the cause of chronic fatigue syndrome, long subfebrile, lymphadenopathy, enlarged liver and spleen.
Parvovirus B19 is known as a cause of infectious erythema, mainly in children. However, from 30 to 60% of adults are seropositive for IgG against B19 virus and infected pregnant, even asymptomatic infection in 16-25% of cases of fetal death occurs ("non-immunological" hydrops) [Chaika V.K. et al., 2006].

Mycoplasma (Mikoplasma hominis, Ureaplasma) – tiny organisms that occupy an intermediate position between bacteria and viruses. They are the causes of miscarriages and premature births. Getting on eye mucosa, respiratory tract, gastrointestinal tract, genitals and they cause neonatal pneumonia, meningitis, conjunctivitis, subcutaneous abscesses.

Chlamydia (Chlamydia trachomatis) – penetrate into the cells, proliferate in them and after their destruction infect neighboring cells. Chlamydia affects 5 million women in the U.S. and 10 million in Western Europe, including the teenage contingent. Infection develops slowly and asymptomatic. In pregnant women it causes urethritis and cervicitis. Also the cause of polyhydramnios, placental insufficiency with developmental delays and fetal malnutrition, abruption placenta, promotes miscarriages and premature birth, but after birth is 4 times more likely to induce the development of endometritis [Nemchenko O.I., 2004]. Chlamydia induce autoimmune processes leading to miscarriage during the early stages of embryo development [Ank Dyska A.S., 1999]. Therefore, plasmapheresis is needed both during pregnancy and even before gestation. Thus O.I.Nemchenko et al. (2004) after the completion of antibiotic therapy is recommended also a course of plasmapheresis in the near menstrual cycle.

Toxoplasmosis is caused by protozoa and also accompanied by a premature termination of pregnancy and high perinatal morbidity and mortality. This disease is also accompanied by autoimmunity and auto-aggressive syndrome, as well as secondary immunodeficiency. In the territories of Russia invasiveness population is 30-35%, and in St. Petersburg among persons aged up to 40 years 31.1% infected. Exacerbation of toxoplasmosis occurs in immunodeficiency states, including at physiological pregnant immunosuppression. When invasion by toxoplasma of pregnant occurs in the first trimester of pregnancy in 75% of fetuses may develop severe pathology with the occurrence of encephalitis and hydrocephalus with subsequent seizures and mental retardation. Much of these children die in the first year of life, and the survivors have severe disabling brain damage [Mardanli S.G. et al., 2005].

Ureaplasmosis also caused by protozoa and is the cause of miscarriage in 29% of pregnant women.

Practically there exists no specific treatment of these infections caused by various pathogens such as protozoa, fungi, bacteria, viruses, especially as they are generally found in association with each other, and often complete combination thereof. Long-term antibiotic treatment of chlamydia (tetracycline, doxycycline, minocycline, erythromycin, ofloxacin, etc.) often leads to severe intestinal dysbiosis and
revitalization of conditionally pathogenic flora with more intensified production of indole, skatole, hydrogen sulfide, which contributes to further strengthening of endotoxemia [Kisina V.I., 1998]. Against the background of pregnancy such therapy is generally unacceptable. It should be borne in mind that any antibiotic represents a potential risk to the fetus, as tests of their embryotoxic or teratogenic effects in pregnant women no holds [Chaika V.K., Demina T.N., 2003].

The primary cause of these chronic infections and, to some extent, even opportunistic, consider weakening the body's defenses women due to past illnesses and various types of exo- and endotoxemia, social factors. However, the appointment of immunomodulators and biogenic stimulants such irrational use cytomedines (thymalin, thymogen, thymoptin) poses a threat of difficulty to control autoimmune processes due to excessive stimulation of T-lymphocytes, and the use of lipopolysaccharide (pirogenal, prodigiozan) stimulates B-cells with increased production of immunoglobulins and antibodies that also can stimulate autoimmune processes [Kisin V.I., 1998].

Therefore, the most reasonable approach to pathogenetically substantiated treatment of these chronioinfections is apheresis therapy aimed at removing those pathological products that contributed to the secondary immunosuppression, as well as quantum methods immunostimulation. Necessary to force the body own fight against these pathogens. Positive results of the use of plasmapheresis in combination with laser irradiation of blood in the treatment of genital herpes and cytomegalovirus infection reported by other authors [Chaika V.K., Shemyakina N.N., 2004; Shemyakina N.N., 2009]. In particular, when used in combination randomized study courses plasmapheresis blood ozonation they reported a decrease in the rate of complications in the period of gestation is 1.8 times, the severity of infection in 2.5 times, premature birth 1.5 times of severe neonatal infection and malnutrition in infants is 2.3 times. T.N.Demina et al. (2009) recommend the use of plasmapheresis in combination with intravenous immunoglobulin, particularly in cases associated viral and bacterial infections.

If there is an associated vaginitis can be carried colposorption is to introduce into the vagina of the same enterosorbent polyphane (lignosorb) as a swab of a single layer of sterile gauze with 10-20 grams of the drug on the night. Such therapy after 3-4 days weakens selection persistently troubled for several months and even years. Such vaginal creates better conditions for the subsequent childbirth.

More stable results gives pair treatment – simultaneous apheresis therapy and husband. In men, these manifestations such chronioinfection are quite scarce, although they may be accompanied by persistent chronic prostatitis. However, if this source is not blocking the receipt of pathogens, it is impossible to achieve a lasting effect in women.
Such complex apheresis and immunostimulatory therapy before gestation provides the best conditions for conception, and in some cases easier and self-conception with infertility caused by, for example, chlamydia. During pregnancy, it provides the best conditions for the development of the fetus and prevents intrauterine infection. It should be emphasized that 83% of infected infants prenatally detected implementation infectious-inflammatory process in the early neonatal period [Red'ko I.I. et al., 2006]. Just before birth provided such prevention of infectious and inflammatory complications.

Ecology and pregnancy

It’s known that in cities with large industrial enterprises, especially the chemical industry, the levels of perinatal mortality is significantly higher than the national average, being one of the reasons for reducing population growth. Added to this dramatic reduction in the category of healthy children, which is not only a medical, social, demographic, and economic importance but. Is not completely safe and the countryside also, where the effects are felt the use of herbicides, insecticides and other pesticides. They are not insured and quite affluent urban residents, taking foods rich in these "additives" include hormones and antibiotics fed to cattle and remain in meat and dairy products. There is an accurate communication of a sanitary condition of the consumed water with child and maternal mortality [Cheng J.J. et al., 2012; Benova L. et al., 2014]. It with special sharpness raises questions of clarification of water and utilization of toxic waste [Onishchenko G.G., 2013].

Among the harmful environmental factors there are a number of chemical compounds known embryotoxic, teratogenic and gonadotropic action. In the first case it is manifested impaired fetal growth (slowing down development, reduction in body weight and size), the second – the advent of his birth defects and congenital malformations, in the third – lesions of the female or male gonads, which is one of the causes of infertility.

Some materials of the book "Pregnancy and toxicants" (1986) about the harmful effects of certain industrial chemicals at the time listed below.

Similar toxicants can collect not only in blood, but also liquid of ovaries follicles, leading to "idiopathic infertility" when even it is impossible to define precisely its reason [Foster W.G., 2003; Mendola P. et al., 2008]. According to the conclusion of the American College of obstetricians and gynecologists (ACOG) in the USA practically each woman is affected by many various toxicants breaking reproductive function including processes of puberty, periods and ovulation, fertility and a menopause [Sutton P. et al., 2012; ACOG Committee Opinion No. 575, 2013].

Increased level of a metilmercury (CH$_3$Hg) and dibenzofurans breaks pre-natal development with cognitive and motor violations, auditory and vision deficiency, to
teeth anomalies. Active tobacco smoking of mother leads to premature birth, fetal growth deficit, damage of kidney tubules and even sudden infant death syndrome. Tetrachlordibenzo-p-dioxin are promoted the early asthma beginning, pneumonia and even lung and breast cancer [Wigle D.T. et al., 2008].

It should be borne in mind the delayed effects of toxic substances. For example, butyl ester does not cause changes in the embryo, but revealed changes in the functional state of births, as well as their subsequent offspring of the first and second generations of the violation of their reproductive function. In addition, nitrites and nitrates contribute to reduce the viability of the first days of postnatal life, and kepone samples and ethylenethiourea cause offspring persistent dysfunction of the central nervous system.

Some pesticides (epoxiconazol) cause a placenta degeneration with the subsequent resorption of a fetus [Rey Moreno M.C. et al., 2013]. In some regions of France such pesticides and their metabolites were found in urine in 5.3%-39.7% of the pregnant women living in such districts [Chevrier C. et al., 2014].

The fetus may be affected by the consequences of the transferred immediately before pregnancy or during the first trimester. For example, after rubella 20% of children may suffer from cataracts or congenital heart disease, 30-35% of children have hearing disorders [McElhaney R.D. et al., 1999].

### Organ toxicity of some industrial chemicals

<table>
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<tr>
<th>Embryotoxicity</th>
<th>Teratogenicity</th>
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We should not forget that many of our life-saving drugs are also chemical agents and their effects on the body of the pregnant and the embryo is not always safe. First we need to recall the terrible talidomid catastrophe 50s, when the reception during pregnancy common in those years and soothing pain medication thalidomide caused the whole epidemic of children born with congenital deformities, expressed mainly in the absence (amelia) and underdevelopment (fokomeliya) one, two, and often all four limbs [Lenz W., 1965]. However, the statistics of the later period also is not optimistic. Thus, according to H.L. Mafenson et al. (1974), in the U.S., about 7% of the newborns had abnormalities, and just over 15 million people had different birth defects. Of these, only 10-15% in the etiology of anomalies were found genetic factors and 3% – chromosomal abnormalities.

In our time, as not all drugs are safe for pregnant and fetal organisms. So widespread antidepressants – imipramine and amitriptyline potentially teratogenic, causing a cleft lip, cleft palate, encephalocele and hydrocephalus. Tetracycline is capable of inducing breach of tooth enamel and tooth formation. Meprobamate causes
mental retardation in children. Salicylates, and in particular, well known, acetylsalicylic acid (aspirin), are also embryotoxic agents. Phenothiazines may cause the development of neonatal jaundice. Streptomycin, taken in late pregnancy, may be the cause of hearing disorders up to a full deafness in children. Phenylbutazone, oxyphenbutazone, tolbutamide responsible for the development of newborns toxic thrombocytopenia. Embryotoxic effects have benzodiazepines (diazepam, seduksen, Relanium, Valium). Diethylstilbestrol, women take during pregnancy can cause girls born 11-15 years after the occurrence of vaginal adenocarcinoma..

In certain cases prolonged hormonal therapy by dexamethasone finds application at detection of signs of a virilization of a female fetus – so-called "transplacentary hormonal therapy". However it is fraught with development in such children in further verbal and cognitive frustration [Hirvikoski T. et al., 2007].

All this made J.M. Rao and R. Arulappu (1981) assume that:
- Effect of the drug on the fetus does not always coincide with the well-known pharmacological effect in the body of the mother;
- Some drugs can have long-term effects on the fetus with the advent of disorders in the later stages of ontogeny;
- **No medicine is completely safe for the developing fetus.**

However, overwhelming desire of doctors to treat and pregnant to cure themselves causes some to prescribe and take other (including their own, without consulting with doctors) a lot of drugs, each of which is far from indifferent to the fetus. Intrigue is in their long-term effects, which are sometimes difficult to relate to their admission episodes during the mother's pregnancy. And in our time when reading the histories in the departments of pathology of pregnancy maternity hospitals in some cases it was possible to count up to 20 (!) varieties of medicines designated pregnant for various indications. Most often, this amount of medicine was prescribed in toxicosis and threatened abortion. However, in most of these cases, instead of introducing new chemicals would need to take away the body of harmful and toxic metabolites.

Thus, only the apheresis therapy able to remove these pathological products of exogenous origin, as incorporated in the course of employment in hazardous occupations, and as a result of residence in the contaminated areas.

In cases of infertility caused gonadotropic substances also shows pairwise treatment. If there were indications from getting embryotoxic and teratogenic compounds, apheresis therapy should be carried out before gestation, because we know that as a bookmark main organs and systems, and their development defects are formed in the first trimester of pregnancy. It should be borne in mind that during the first 12 weeks, the trophoblast has not yet emerged a reliable barrier function, so it is in the first trimester of pregnancy are particularly dangerous potential embryotoxic and teratogenic substances, including many drugs [Chaika V.K., Demina T.N. , 2003].
Comparative studies carried out by us in comparable climatic and demographic conditions, but differing in the concentration of industrial cities of the Volga region, showed that in ecologically unfavorable conditions, the frequency of preterm birth, late toxicosis of pregnancy, perinatal mortality and neonatal morbidity prevailed twice. Similarly, 2-3 times had a higher incidence of respiratory diseases and ENT, allergies, as well as group of often chronically ill children in the first years of life [Voinov V.A. et al., 1996].

This indicates that in areas of environmental stresses under pregnant double press of toxic products, such as endogenous and exogenous origin. Thus, even in the absence of actual evidence of toxemia of pregnancy, ecotoxicosis creates the same unfavorable conditions for ripening fetus. Say the same and found disorders of a biochemical and immune homeostasis of children and the general population in such industrial centers.

In particular this applies to signs of exhaustion or suppression of the antioxidant defense system, as well as immune deficiency. It testifies that formed in utero immune deficiency persists in later life. The second and subsequent generations in such conditions become even less resilient, which is manifested in the growth of the so-called cumulative incidence of children, traced in the same place for the last 30 years, and it already can significantly change the demographic situation in the future.

In the research conducted by I. M. Morozova (1998) it is noted that only 7,5% of children with allergic diathesis had a physiological course of pregnancy of their mothers. More than at a half of these women pregnancy was complicated preeclampsia, to a lesser extent by pregnancy not incubation threat. The complicated course of pregnancy made an adverse effect on immune system of a fetus. At such children who were born from mothers with preeclampsia the immunogram for the 5th day of life was characterized by the raised maintenance of CD4 of a ratio of CD4/CD8. At the children born from mothers with not incubation threat decrease in functional reserves of neutrophils and increase of level of seruman IgG and IgA are revealed.

There is no doubt greater risk of poisoning and more pronounced severity of intoxication during pregnancy for most expectant mother. In particular, experimental studies have found that pregnancy complicated by chronic intoxication, leading to more serious liver problems than conventional toxic hepatitis [Taskaev I.I., 1979].

All of these above facts underscore the urgency of preventive detoxification, both before and during pregnancy in cases where we can expect morbidity and fetal abnormalities. Of particular significance in these activities acquire guidance on adverse outcome during of previous pregnancy.
Hemolytic disease of the fetus and newborn known since 1609, but only after the discovery of Rh-factor in 1940 was the clear nature of this pathology. Nowadays this term hides many kinds immune conflicts between mother and fetus, because now there are more than 10 systems isoserological red human blood, and many of them still further divided into several subspecies. Apart from the known ABO antigens and Rh, there are known Kell factors, Duffy, Kidd, Lewis, MNSs and many others. Virtually everyone has their own individual set isoantigens, which may be identical only in identical twins. As a child isoserological usually combined features of both parents, a priori, we can assume that the mother and fetus isoantigens never sets can not match and potentially immune conflict possible on this basis, although really the greatest practical importance attaches to the conflicts between the Rh-negative mother and Rh-positive fetus with the formation of maternal antibodies to fetal antigens.

Thus, Rh antigens Rh-positive fetus during pregnancy gradually penetrate the placenta and cause an immune response in the mother, the antibodies which also penetrate through the placenta into the fetal circulation, causing damage of erythrocyte membranes and chronic hemolysis. Last contributes to the accumulation of bilirubin with impaired kidney, liver and brain. Progressive anemia aggravates tissue hypoxia. Damage to the liver leads to portal hypertension and ascites, hepatocellular damage barrier development hypoalbuminemia and generalized edema tissues (fetal hydrops), which determines the high level of stillbirth in Rh incompatibility to 18%. Pregnancy complicated by Rh-conflict occurs pathologically, against the threat of termination of pregnancy (56%), placental insufficiency (73.8%), syndrome of intrauterine growth retardation (70.2%), polyhydramnios (34.5%), promotes disruption of blood coagulation potential, hyperactivation of coagulation system with the development of chronic DIC [Klimov V.A. et al., 2004].

In the first pregnancy notable concentration of Rh antibodies and subsequent violations chain occurs to the 20th week and the baby can still be born alive, but in a state of severe hemolytic disease of the newborn (HDN) requiring intensive care for serious measures, which will be discussed below. Repeated pregnancy begins at a sufficiently high initial titre and to the 20th week can already come a critical concentration, which leads to the fetus in utero death of dropsy, or the death of a newborn jaundice [Bowman J.M., 1998].

No less serious conflicts also can be at a different group membership, for example, if A and/or B antigens in the fetus and β and/or α antibodies of mother [Zauralskiy R.V., Dolgoshapko O.N., 2009].

In such immune conflict - prone development of hemolytic disease of the fetus in recent years is widely used method of intrauterine fetal blood exchange transfusion, which enables timely to reduce dangerous levels of antibodies and prolong pregnancy. However, such interventions are carried out to a certain extent "blind", can cause fetal injury with episodes of bradycardia and asystole until his death in utero. Moreover, the
possible bleeding in the mother and fetus may enhance the immune response [Konoplyannikov A.G. et al., 1999].

Even the clinical introduction of RhD-alloimmunization, completely not eliminates this problem [Lubusky M., 2010].

The severity of pathological disorders of the fetus necessitates measures to timely removing of maternal antibodies to fetal red blood cells. The most effective method of efferent therapy in these cases is plasmapheresis [Vyugov M.A. et al., 2003, 2012; Fedorova T.A., 2003]. Overseas experience also shows the effectiveness of such sufficient plasmapheresis held weekly – to 20 or more sessions during the pregnancy [Hanafusa N. et al., 2007]. Thus for each removed again up to 4 liters of plasma, ie 1.5-2 CPV. Maintenance used successfully periodic sessions of plasmapheresis followed by immunoglobulins until a period of 37 weeks of pregnancy [Palfi M. et al., 2006; Novak D.J. et al., 2008; Isojima S. et al., 2011].

In rare cases, there is incompatibility minor blood group antigens of the group P. Fetal antigens such groups already in the third week expressed on trophoblastic tissue of the placenta. Maternal anti-P antibodies recognize these antigens and disrupt the function of the placenta, slowing fetal development and lead to early miscarriage. N.Hanafusa et al. (2006) using the long course cascade plasmapheresis treatment each time 3-4 liters of plasma, and spent a total of 57 such sessions provided by the 37th week of pregnancy, the birth of a healthy girl weighing 2496.

G.D.Wool et al. (2014) on the 17th week of pregnancy of a background of the Rh-conflict found out severe haemolytic anemia of a fetus that caused the necessity of carrying out 50 sessions of a plasma exchange with birth on the 37th week of pregnancy of the viable child. Thus for every time 1.5 - 2 CPV are removed to 4 liters of plasma, ie. With success periodic carrying out sessions of a plasma exchange with the subsequent introduction of immunoglobulins up to achievement of term of 37 weeks of pregnancy is used [Palfi M. et al, 2006; Novak D.J. et al., 2008; Isojima S. et al., 2011]. Well timed carrying out courses of a plasma exchange with intravenous administration of immunoglobulins excluded need of pre-natal blood transfusion [Bellone M., Doctor F.N., 2014; Fernández Alba J.J. et al., 2014; Kamei K. et al., 2014].

Even if you use anti-Rhesus immunoglobulin preliminary course plasmapheresis stabilizes the fetus by reducing the amount of degradation of its erythrocytes that can prevent the development of severe hemolytic disease of the fetus [Mitrja I.V. et al., 2011]. Neonatal deaths in the early neonatal period were not in any case, while in the comparison group, this figure was 14.6%. Significantly more frequent in hemolytic disease of the fetus mild and moderate (61.1% and 38.9% versus 10.4% and 75% respectively), and blood exchange transfusion took only 13.9% neonates versus 27 % in the comparison group.

Reimbursement of donor plasma volume and protein preparations warns hemodynamic disorders and both mother and fetus during plasmapheresis, but
undoubtedly is an irreparable loss of *progesteronum*, and after the 8th week – placental hormone human *chorionic gonadotropin*, which was supposed to be accompanied by excitation of uterine muscle activity and contribute to interrupt gestation. Nevertheless, this does not happen, which means extremely flexible and reinsures compensation system regulatory homeostasis components removed of highly reliable system autoregulation when reducing the concentration of a hormone or enzyme is accompanied by immediate release into the circulation of the respective ingredients from the depot. This is most eloquently emphasizes security operations plasmapheresis, which really is not accompanied by any significant shifts in hormonal, enzymatic, mineral, protein, lipid metabolism, hemodynamics and gas exchange disorders, disabilities of any organs.

In the presence of Rh-conflict history it is necessary preventive removal of antibodies from the blood of women before pregnancy should be assumed that the achieved rate of four sessions of plasmapheresis and is accompanied by an almost complete disappearance of such antibodies. In the course of pregnancy requires more careful monitoring and preventative plasmapheresis at the slightest tendency to an increase in antibody titer. Such tactics can only guarantee the prolongation of pregnancy to term and birth a full healthy baby [Voinov V.A., 2013].

There is another circumstance in favor of apheresis therapy in such cases. As you know, the placenta normally transmits only low and MIDDLE weight products and should block the transition "whole " protein molecules (especially immunoglobulines) as the maternal and fetal side. Therefore, no antigens or antibodies would not have to cross the placental barrier and theoretically, no Rh or antigenic group conflicts during pregnancy should not happen. And indeed, there are cases complete incompatibility Rh and group affiliation of mother and fetus, which, however, are not accompanied by conflict. And antigens and antibodies are able to penetrate through the placental barrier in cases of increased permeability of the vascular endothelium in endotoxemia. Therefore, preeclampsia can contribute to both the appearance and severity of such potential conflicts. Apheresis therapy of preeclampsia in such cases can help smooth isoserological reactions, and plasmapheresis in rhesus automatically promotes correction and endotoxemia also.

**Miscarriage and infertility**

The problem of miscarriage is still one of the most urgent problems of obstetrics. Its frequency is 15-20% of all pregnancies, and the frequency of infertility – in 5-11% of marriages. In 30-40% of these abortions are "unexplained" [Kutteh W.H. et al., 1999].

Among the etiological factors observed anatomical abnormalities of female genitalia, chromosomal pathology, infectious disease, neuroendocrine pathology,
antiphospholipid syndrome. We shall mention only those in whose elimination can be used apheresis therapy.

Virtually all of the above complications of pregnancy to some extent also threaten miscarriage or premature birth. It is characteristic of preeclampsia and enhancing hidden genital infections, and Rh-conflict. In all these cases the pathogenesis of disorders is reduced to the accumulation in the body of a pregnant pathological products and apheresis therapy that promotes their excretion, and provides the best conditions for the continuation of pregnancy.

Often threatened abortion occurs due to inadequate treatment as in the case of ovarian hyperstimulation syndrome, and these situations could also be eliminated with plasmapheresis

Cause late miscarriages and intrauterine be "bullis" infection of the fetal capsules with the development of chorioamnionitis and exudative effusion in the placenta and umbilical cord, and then the fruit itself. In placental hemorrhage occur with edge placental abruption with acute disorders of uteroplacental and fetoplacental circulation. Infection of amniotic fluid leads to rising microbial colonization of the airways and lungs with the development of bronchiolitis and perifocal interstitial pneumonia. Among the pathogens they can note *Staphylococcus aureus, Enterobacter, yeast Candida, Klebsiella, Pseudomonas aeruginosa* and *Corynebacterium*.

However, the causes of miscarriage may be autoimmune mechanisms. Sex hormones play a different role in the pathogenesis of autoimmune diseases. In animal experiments established that estrogens provoke some autoimmune processes affecting steroid receptors in specific CD8+ T-lymphocytes and CD5+ B-lymphocytes. However, autoantibodies are present in sera of patients with or without symptomatic autoimmune disease. Abnormal levels of autoantibodies may be accompanied by not only obvious, but also preclinical or subclinical autoimmune disorders. This concept has been supported by the discovery of abnormal autoantibody levels in a group of clinically healthy women who were, however, different forms of reproductive disorders. These women have the large number of different autoantibodies accompanied repeated "habitual" miscarriage, endometriosis, early ovarian function disorders, unexplained infertility, in vitro fertilization and embryo implantation failure [Geva E., et al., 1997].

**Antiphospholipid autoantibodies (APA).** It is known their relationship not only with recurrent venous and arterial thrombosis (pulmonary embolism, Budd-Chiari syndrome, thrombosis of the renal veins), but also with the recurrent spontaneous abortions, intrauterine fetal growth arrest, "missed abortion", preeclampsia, thrombocytopenia. APA most often include two types of autoantibodies - *anticardiolipin* and *lupus anticoagulant*. They are found also about 2% of women with normal pregnancy [Lockwood C.J. et al., 1989]. At the same time, in pregnant women with preeclampsia incidence of antiphospholipid antibodies reaches 63.5%
[Ponomarev I.V. et al., 2000], and the combination of intrauterine growth retardation with hypertensive disorders in pregnancy, this rate reaches 90% [Chaika V.K., Demina T.N., 2004].

Non-organ specific autoantibodies and, especially, APA, are one of the causes of recurrent miscarriage. Immunopathogenetic mechanism which leads to early miscarriage in patients with AFA may be determined by the utero-placental thrombosis and vasoconstriction due regard membrane phospholipid antibodies as endothelial cells and platelets. This reduces the production of prostacyclin by endothelial cells, increased platelet thromboxane production, reduced the activity of C-protein, which is a physiological anticoagulant inactivating procoagulants – factor Va and VIIIa [Kutteh W.H. et al., 1999]. This leads to instability of the membrane and increase platelet aggregation and inhibition of endothelial prostacyclin synthesis. In addition, the process can cause inhibition of prekallikrein and endothelial release of plasminogen. It may also affect the process of implantation of embryos at the endometrium.

N. Gleicher et al. (1994) also investigated the relationship between unexplained infertility and miscarriages with autoimmune disorders. Autoantibodies were detected such as lupus anticoagulant antibodies to cardiolipin, phosphatidylserine, phosphatidylethanolamine, histones to DNA, polyninosinic and polidioxythymidic acids – in 88% of patients with infertility and 70.8% with miscarriages. And they reported unusual frequency gammopathy (type IgM) in 38.5% and 45.8% of these patients, respectively. They concluded that some patients with unexplained infertility and miscarriages suffer polyclonal activation of B-lymphocytes and thus confirmed a causal relationship with this autoimmune disorders obstetric pathology. Even in cases where autoantibodies for some reason can not be determined, increased 1.5-2 times the level of the CIC may also indirectly indicate an autoimmune nature of "unexplained" infertility [Lubyanaya S.S. et al., 2006].

It is usually assumed that the spontaneous abortions in the first trimester of pregnancy are the result of chromosomal abnormalities. However, damage to the antiphospholipid antibody of cell membranes phospholipids villous trophoblast "opens" for their cytotoxic effects of maternal immune cells in the first trimester to the 8th week of pregnancy [Hasegava I. et al., 1990]. Circulation antiphospholipid antibodies often found in the group of early miscarriage in 43.1% of patients in the group, and even earlier pre-embion loss (35.7%) than in the group of late miscarriage (22.4%). Characteristically, most of these women initially treated for infertility, while 15% of them have been repeated attempts in vitro fertilization [Makatsaria AD et al., 2003].

Clinical studies have shown that the causes of early miscarriages were not anticardiolipin and antiphosphatidilserin but antiphosphatidylethanolamine antibody. Phosphatidylethanolamine is one of the major components for both peripheral and inner layers of the cell membrane. However, these specific antibodies contribute not so much direct damage phosphatidylethanolamine but much damage high molecular
weight kininogen, factor XI or prekallikrein. In this kininogen-dependent antibodies stimulate antiphosphatidylethanolamine trombin-induced platelet aggregation [Sugi T. et al., 1999].

Histologically revealed pronounced signs peri-villous thrombosis, emptiness of vascular terminal villi, their chronic inflammation [Salafia C.M. et al., 1997]. In addition to thrombosis and hemorrhage detected in inter-villous spaces retro-placental hematoma, extensive placental infarction and necrosis. This leads to early thrombosis of utero-placental vessels with nutrition disorders and death of the embryo. Besides influence violations receptor function of endothelial cells and trophoblast, as well as the impact of intrauterine autoantibodies affecting the embryonic development of the fetus and also are the cause of repeated implantation failures that do not rightly interpreted as infertility [Taylor P.V. et al., 1989; Birkenfeld A., Mukaida T. et al., 1994]. In addition to blood supply and fetal nutrition disorders, it can happen the direct effects of antiphospholipid autoantibodies also. So, L.F. Akanli et al. (1998) described five cases of cerebral infarcts in newborns whose mothers showed increased concentration of anticardiolipin antibodies.

Antiphospholipid antibodies can bind to the cells of the trophoblast and hurt them in violation of the placental barrier, which becomes passable for CIC, viruses, bacteria, and auto-antibodies isoimmune. Antiphospholipid antibodies are a class of IgG-globulin and cross the placenta, giving the fetus the same effect as in the mother's body [Sidelnikova V.M., 2005]. Transplacental transfer of maternal antibodies to the fetus can cause vascular thrombosis of any location, including the aorta, renal arteries, cerebral arteries and the superior sagittal sinus, in the portal system. While antiphospholipid antibodies in the blood of the newborn may be delayed for a period of 3-6 months. On the other hand, in the "reverse" direction through impaired placental barrier can penetrate fetal antigens that promote sensitization with the development of fetal maternal antibodies, which further exacerbates the development of the fetus.

Surface of the apical membrane of placental villi facing the uterine intervillous circulation, normally covered by special anticoagulant protein – Annexin-V. In studying these villi in the placenta at caesarean section extracted, J.H.Rand et al. (1997) found that in patients with antiphospholipid syndrome annexin-V content is significantly lower than in healthy women. During the incubation of tissue culture placental villi of normal placentas with antiphospholipid IgG for 24 hours showed a significant decrease of this apical annexin-V. Furthermore, it was founded inhibition of cell proliferation of human umbilical vein endothelial cell culture containing anticardiolipin antibodies [Arakawa M. et al., 1999].

Available block Annexin-V specific anti-annexin-V antibodies are described in connection with recurrent miscarriage and systemic lupus erythematosus. These antibodies can facilitate the transition of anionic phospholipids from the inner to outer cell membranes promote apoptosis umbilical vein endothelial cells. Thus there is a way
out procoagulant phospholipid membranes – phosphatidylserine [Cheng H.-M., 1997]. Such "externalizing" phosphatidylserine upon activation of platelets and macrophages leads to activation of their surface coagulation factors X and V, and prothrombin also [Vogt E. et al., 1997]. Removal of annexin-V under the influence of antiphospholipid antibodies on the surface of trophoblast makes it procoagulant. In addition, they depress the formation of syncytia, hormone production and invasion of the decidua. The result is a placental insufficiency, leading to stop development of the fetus, preeclampsia and abortion [Rote N.S., 1997].

In antiphospholipid syndrome prematurity observed in 2.5 times more frequently, in 3 times more common hypotrophy in infants and all cases of hypotrophy III degree [Ponomarev I.V. et al., 2000]. The antiphospholipid syndrome contributes also to a severe preeclampsia [Romano G. et al., 2007]. At preeclampsia on the background of antiphospholipid syndrome in 71.5% of cases there were signs of placental insufficiency with intrauterine fetal retardation development. Failure of implantation of embryos in vitro fertilization explains the possibility of ovarian hyperstimulation effect – stimulating action of high doses of estrogen on the development of autoantibodies.

Besides, development also a so-called catastrophic anti-phospholipid syndrome with the serious progressing multiple organ insufficiency is possible [Makatsaria A.D. et al., 2003]. At development of such complication apheresis therapy, including a plasma exchange is expedient [Schlembach D. et al., 2012].

The myocardial infarction arising in the postnatal period can be connected with the accompanying antiphospholipid syndrome [Krishnamuthy M. et al., 2004], though also the consequence of a secondary endotelialny sensitization fetal anti-genes is possible, and the plasma exchange is also capable to stop it [Houck P.D. et al., 2012].

Because the pathogenesis of complications of pregnancy in antiphospholipid syndrome plays a leading role hypercoagulation, the widely used anticoagulant and antiplatelet drugs on the background of corticosteroids. Nevertheless, the conventional therapy with corticosteroids suppress immunological reactivity and correction of hemostatic anticoagulants and antiplatelet agents are not always effective and fraught with acute exacerbation of chronic endometritis with the risk of intrauterine infection of the fetus. Moreover, there is evidence that glucocorticoids administered to a pregnant woman may help to delay the growth and development of the fetus, which was confirmed in special experiments on animals [Jobe A.H. et al., 1998].

Failures with implantation of extracorporeal impregnated embryos B.Fisch et al. (1991) explained with possible effect of hyper stimulation of ovaries – the stimulating influence of high doses of an estrogen on autoantibodies development. They determined the APA level during an early follicular phase, during the expected peak of the E2 level and 14 days later after of an ovum extraction. But these finds show also the APA high initial level even before treatment.
As in pathogenesis of complications of pregnancy at an antiphospholipid syndrome the leading role is played by hyper coagulation, anticoagulants and disaggregant against corticosteroids are actively used [Sapina T.E., Mishchenko A.L., 1999]. Nevertheless, the standard therapy of suppression of immunological reactivity corticosteroids and corrections of violations of a hemostasis by anticoagulants and disaggregant isn’t always effective and fraught with an exacerbation of a chronic endometritis with risk of pre-natal infection of a fetus. Moreover, there are certificates that the glucocorticoids entered to the pregnant woman can promote a growth inhibition and developments of a fetus that is confirmed also in special experiments on animals [Jobe A.H. et al., 1998].

Antiphospholipid syndrome, in addition to the danger of recurrent miscarriage, may be accompanied by pulmonary vessels thromboembolism in the development of thrombophlebitis of deep vein of the lower extremities and pelvis, the frequency of which is from 1.5 to 2.7 per 1,000 pregnant women and from 2.8 to 18.3% in of maternal mortality [Makarov O.V. et al., 1999]. Antiphospholipid syndrome and predisposes to severe preeclampsia [Romano G. et al., 2007].

S.A. Laskin et al. (1997) attempted to use prednisone and acetylsalicylic acid in pregnant women with antiphospholipid syndrome and do not succeed, because the frequency of live births, not significantly increased, but premature in the main group was 62% compared with 17% in the control. In addition, there is information on the effects of aspirin on the fetus, causing hemorrhagic condition in newborns. Moreover, more likely to develop hypertension (13% vs. 5%) and diabetes (15% versus 5% in control group).

S. Cowchock (1997), leaving the possibility of the use of heparin in the presence of signs of thrombosis, urged caution with the appointment of prednisone and immunosuppressive therapy (including immunoglobulins) in pregnancy. Efforts were even attempts to use traditional Chinese therapy, which led to some reduction of antiphospholipid antibodies [Takakuwa K. et al., 1997].

It should be emphasized the dangers of hormone therapy during pregnancy. Thus, G. Celsi et al. (1998) have shown that the penetration of glucocorticoids across the placenta contribute to slow fetal growth and the emergence of hypertension in them as adults. Described dysfunction of the hypothalamic-pituitary-adrenal system in children whose mothers received during pregnancy hormone therapy. This was confirmed in experiments in which the use of dexamethasone in pregnant animals led to a decrease in neonatal weight, malnutrition and reducing renal glomeruli compared to the control. It is believed that decrease the number of nephrons reduces the area of glomerular filtration rate that contributes to the development of essential hypertension. Obviously, this explains the higher blood pressure (130±4 vs. 107±1 mmHg in the control) in the experimental animals were born.
G. Framton et al. in 1987 described a case of when, after 10 (!) unsuccessful attempts to maintain the pregnancy only after the introduction of plasmapheresis in the range of therapeutic interventions managed to prolong pregnancy up to 34 weeks with the happy delivery. Later D. Fulcher et al (1989), also after repeated unsuccessful attempts to save the pregnancy and fetal life using prednisone and aspirin, have succeeded only with the help of six sessions of plasma exchange, which led to a significant reduction of anticardiolipin antibody levels and stabilized placental blood flow, followed by a live birth.

Experience Scientific Center for Obstetrics, Gynecology and Perinatology [Rogachevskiy O.V. et al., 2005] in the treatment of 147 patients using plasmapheresis showed the possibility to obtain a reduction of activity of the autoimmune process with a significant decrease until the complete disappearance of lupus anticoagulant, CIC levels (26%) and immunoglobulin E, F, G (for 16-21%), normalization coagulogram, paramecium survival time, disappearance of markers of DIC. Normalized indicators of oxygen transport, PaO₂ and hemoglobin oxygen saturation. In 76% of these patients took timely delivery, and at 6 % for period 32-34 weeks with weighing 2.6-3.9 kg newborns, and all the children were alive. Moreover, it was useful to introduce a course of plasmapheresis (three times in a day) in the scheme of preparation for in vitro fertilization and embryo transfer in 62 women with tubal-peritoneal infertility also. Percentage of pregnancy based on one embryo transfer with 51.6%, while in the comparison group (50 women who carried only medical therapy) – 42% (p<0.05). Of pregnancies ended in childbirth 84.4% (with 71.4% in the comparison group, p<0.05), with the birth of viable children in 100% of patients. After the preparation for IVF with plasmapheresis incidence of ovarian hyperstimulation syndrome was 8%, while in the comparison group, it developed three times as likely (28%) [Fedorova T.A. et al., 2004].

In the Donetsk regional center of maternity and childhood (Ukraine) courses of plasmapheresis were performed in 80 pregnant women with antiphospholipid syndrome who have managed to get 78 (97.5%) of viable children, while in the comparison group (60) had been interrupted 14 pregnancies (23.3%) in the I trimester, 10 (16.67%) – in the II trimester, 5 infants died of respiratory distress syndrome and cerebrovascular accidents [Demina T.N. et al., 2004]. Moreover, courses of plasmapheresis in 33 women with preeclampsia on the background of antiphospholipid syndrome contributed cupping hypercoagulable syndrome with decreased levels of fibrinogen by 17%, normalization of prothrombin index, activated thrombin time, decreased platelet aggregation by 18%, and lower levels of markers of DIC – D-dimer and fibrin monomer complexes by 2.5-3 times, while in the comparison group (30 women with traditional drug therapy) was only observed a trend towards normalization of these parameters [Chaika V.K. et al., 2004].
Positive results plasmapheresis marked by other authors [Belenky L.M., Serkov V.F., 2003; Linnikov V.I., 2004; El-Haieg L.O. et al., 2007; El'skaja S.N., 2009], as well as on our own experience. K. Abou-Nassar et al. (2010) in a patient with systemic lupus erythematosus plasmapheresis used prophylactically monthly throughout pregnancy with birth of a healthy baby.

Many researchers believe lead antibodies to \(\beta2\)-glycoprotein I in the genesis of thrombophilia. Wherein the most frequently and more difficult runs preeclampsia also [Sidelnikova V.M., 2005].

**Antinuclear autoantibodies (ANA).** ANA frequency among women with recurrent spontaneous abortions ranges from 8 to 50%. Abortion can occur during or after I trimester. ANA may be only markers of the presence of other autoantibodies also.

**Anti-DNA antibody.** They are found in 5% of women with unexplained abortions, compared with the total lack of abortion in explicable. N. Gleicher et al. (1994) found these antibodies in 18.4% of women with unexplained infertility and 29.2% of women with unexplained abortions.

**Rheumatoid factor.** Rheumatoid arthritis affects women more often than men, and this is obviously also affect the course of pregnancy. Thus, according to S. Shulman (1986) of 54 women who developed rheumatoid arthritis after marriage, had an average of 1.4 live birth, compared with 2.3 in the control group. According to some reports, 70% of women with rheumatoid arthritis, had no pregnancy at all [Ivanov I.I. et al., 2008].

**Antithyroid antibodies (ATA).** They are found quite often in the healthy population, especially in women of reproductive age. Most often it happens against the background of other autoimmune disorders. Thus, ATA was detected in 45% of women with systemic lupus erythematosus. D. Glinoer et al. (1991) found a specific association between the presence of ATA and spontaneous abortions (13.3% versus 3.3% in the control group), and according to W.H.Kutteh et al. (1999), the ratio was 22% and 14% respectively. Inadequately treated hypothyroidism, resulting in anemia, preeclampsia, placental abruption, may help to delay the development of the fetus, miscarriage and premature birth, postpartum hemorrhage [Varlamova T.N. et al., 2000]. These data indicate a possible role of these autoantibodies in the pathogenesis of recurrent miscarriage also.

**Anti-ovarian antibodies (AOA).** They can damage the structure of various ovarian cell surface membranes including, corpus luteum, oocytes (ova) and certain interstitial cells of the ovary. Described autoimmune oophoritis with lymphocytic infiltrates, cystic follicles and atresia. AOA was detected in 22.7% of women with primary infertility and 37.5% – with secondary infertility included in vitro fertilization program. AOA detected communication with endometriosis and subsequent failures with implantation embryos also. AOA can also occur during in vitro fertilization
programs as a result of repeated hormonal stimulation and ovarian micro-traumas when retrieving eggs. Immunosuppressive therapy in some cases permit to normalize the menstrual cycle and even provide the subsequent development of pregnancy.

**Antibodies to smooth muscle (ASM).** In the presence of healthy individuals in the population from 2 to 20%, found their relationship with spontaneous abortions and infertility also. Persistent viral infection is one of the reasons for production of these autoantibodies. In women with infertility ASM detected in 49%, compared with 17% in the control group. ASM can cause violations of tubal patency also.

In the genesis of miscarriage may play a role also the antibodies for determining such autoimmune bowel diseases like Crohn's disease and ulcerative colitis, occurring in persons 20-35 years, ie of childbearing age. Found that these diseases observed a higher risk of preterm birth at gestational ages up to 33 weeks, low birth weight (less than 1,500 g), and the greater frequency of caesarean section [Kornfeld D. et al., 1997].

**Antibodies to chorionic gonadotropin (ACG).** It is known that since 8-10 weeks of pregnancy its development depends upon the hormonal activity of the placenta. It chorionic gonadotropin reduces immune activity of the parent body, preventing rejection of the fetus as a homograft. ACG block its activity with a decrease in hormone production of placenta – placental lactogen, estradiol, progesterone, and that poses a threat of spontaneous abortion [Sidelnikova V.M., 2005]. In addition, it is possible development of chronic DIC with a tendency to hypercoagulability when placental blood vessels are formed from multiple thrombosis of placental insufficiency and placental abruption. Injured placenta no longer prevents the penetration of the fetal circulation of toxic products, which accelerates the onset of fetal death [Chaika V.K., Demina T.N., 2003].

There is evidence of the possibility of antibody formation using gonadotropins used for therapeutic purposes, in particular in the program of assisted reproductive technologies. Such antibodies are detected within a few months after the miscarriage. Also it noted the development of long-term amenorrhea in women with ACG due to cross-reactivity with luteinizing hormone. Thus I.D.Gyulmamedova et al. (2004) reported the presence of 70% ACG in the secondary female infertility, whereas they are not detected in women with primary infertility. 23% of the observed there was combination with elevated levels of ACG and sperm antibodies. Application rate of plasmapheresis with subsequent use of in vitro fertilization contributed to pregnancy in 6 women (50%). The same tactics used T.N.Demina et al. (2004). In this repeated courses of plasmapheresis were performed in 1-1.5 months under the control level ACG until 36 weeks gestation. After rate plasmapheresis there occurs reduction of titer IgM and IgG to normal levels or weakly reactions, indicating a significant decrease in the activity of the autoimmune process, and risk of fetal loss [Ochan A.S., Fedorova T.A., 2007]. Development of placental insufficiency was observed only in 4 of 18
patients. Thus, an attempt to limit the introduction of immunoglobulin treatment or hormones (Duphaston) gave worse results than using plasmapheresis [Bichevskaja R.G. et al., 2006].

Increased levels of antibodies to the protein S100, regulating apoptosis and migration of neuroblasts of the brain and spinal cord and their functional differentiation, often accompanied by intrauterine fetal death, and for prolongation of pregnancy may be a cause of neural tube defects in the fetus and the birth of children with cerebral palsy [Poletaev A.B., 2010]. HPV infection induces increased synthesis of these antibodies on the mechanism of molecular mimicry.

Endometriosis affects 15-20% of women of childbearing age. In 25-40% of women with endometriosis develops infertility [Rozhkovskaya N.N. et al., 2008; Barañao I., 2014]. When this process occurs tissue overgrows histologically similar to the endometrium, outside the boundaries of the normally located uterine lining. In normal endometrial tissue fragments trapped in the abdominal cavity with a retrograde flow of menstrual blood to be destroyed by known immune mechanisms, including through the formation of antibodies to endometrial elements. If their destruction and elimination does not happen, they can be implanted in different parts of the peritoneum. In such cases, autoantibodies may persist and violate not only the ectopic "implants", but the endometrium in the uterus, which is especially dangerous during the implantation of the fetus.

IgG and complement penetrate the endometrium of women with endometriosis and the antigen-antibody reaction in the uterine cavity can affect the processes of embryo implantation and cause high rates of spontaneous abortions in this disease. Even with organic causes of infertility (tubal pathology) in addition can be concomitant subclinical autoimmune disease [Geva E., et al., 1997].

Studies in recent years show the association of endometriosis and violations of both humoral and cellular immunity involving T- and B-lymphocytes, natural killer cells, macrophages. There is marked accumulation of these cells in the endometrium. In the peripheral blood of patients with endometriosis there are also detected the autoantibodies to autologous endometrial tissue [Ulukus M., Arici A., 2005; Barañao I., 2014]. Marked accumulation of these cells in the endometrium. In the peripheral blood of patients with endometriosis also detect autoantibodies to autologous endometrial tissue [Kujawskaja D.V., 1999]. And this is not unusual, because the immune system already produces antibodies to have ectopic endometrial elements. As much as their antigenic structure identical normally located endometrium, the latter also regularly exposed to these autoantibodies. It is possible that any matter disorders and most peritoneal implantation in the field of endometrial cells, as in-vitro experiments endometrial elements fixed to only those portions of the peritoneum, which were damaged epithelium layer [Groothuis P. et al., 1999].
Apparently, endometriosis has significantly more widespread than expected. Thus, J. Balasch et al. (1996) at 45-50% laparoscopy in women with low subfebrile or pelvis pain, and in the absence of any symptoms showed signs of endometriosis.

In the study of peritoneal fluid revealed signs of "oxidative stress", which resulted in oxidized lipoproteins are antigenic and can also cause autoantibodies. Such autoantibodies to oxidized proteins detected in patients with preeclampsia and even coronary disease. Women with endometriosis also exhibit autoantibodies to these markers of oxidative stress [Shanti A. et al., 1999].

Autoantibodies to phospholipids (cardiolipin), histones and polynucleotides were also detected in approximately 60% of women with endometriosis [Wardle P.G. et al., 1985]. When endoscopic a fluid from the abdominal cavity exhibit significantly increased levels of cytokines (IL-1, IL-6, IL-8, TNF-α), which indicates their role in pathogenesis as endometriosis and infertility in general [Harada T., et al., 1997; Hsu Ch.-Ch. et al., 1997; García-Velasco J.A. et al., 1999]. O. Richter et al. (1998) consider the most important role play TNF-α, whose concentration in the peritoneal fluid of patients with endometriosis was increased 20-50 times compared to the control level in healthy women. Apparently just cytokines stimulate B-cells to release specific immunoglobulins [Odukoya O. et al, 1996].

In endometriosis peritoneal fluid containing elevated levels of cytokines and even lysosomal enzymes has damaging effects on sperm motility reducing – the number of moving cells is reduced to 15%, and their speed is reduced to 8 mm/s (in the control group these indices were 87.7% and 28.3 mm/s) [Gorbushin S.M., 1999].

Thus, at endometriosis, infertility accompanied, plasmapheresis may be helpful, since it is possible to expect reduction of pathological cytokines and autoantibodies, not only in plasma, but also in peritoneal fluid.

One of the reasons "unexplained" infertility can be chronic endometritis, emerging after a long (more than 5 years) use of intrauterine contraception. Typically, this is accompanied by a significant increase in the number of CIC against the background of immunosuppression. Using plasmapheresis courses contributed to the normalization of the immune status and to pregnancy with the birth of viable children [Chaika V.K. et al., 2009].

Polycystic ovary syndrome is also one of the reasons of complications of pregnancy, premature birth, and newborn have considerably smaller body weight and more often demand intensive therapy [Qin J.Z. et al., 2013; Palomba S. et al., 2015]. Often it is followed also by anovulatory infertility, requires both hormonal therapy and methods endosurgical stimulate ovulation, after which it is advisable to perform also a course of plasmapheresis in the complex post-operative rehabilitation. This increased ovulatory function recovery by 11.4%, the reproductive function of 20.6% and the number of births at 25.3% (compared with a group of patients, which was not performed plasmapheresis) [Chaika A.V. et al., 2008, 2009].
But for purely "mechanical" causes of infertility – tubal-peritoneal forms after laparoscopic operations patency of these pathways using plasmapheresis appeared also suitable as an effective therapeutic modality in the composition of such complex therapy [Bakuridze E.M., 2003]. After reconstructive plastic surgery burn surface formed with an increase in metabolism and decay products of coagulated tissue, vasoactive substances, resulting in the formation of autoantibodies and inflammatory complications re adhesions. Conducting sessions of 2-4 therapeutic plasmapheresis and ozone therapy in the early postoperative period, accelerate the process of regeneration and reduction in the subsequent adhesion [Bakuridze E.M. et al., 2003].

It should be noted that after the operations, such as myomectomy, preventive courses of plasmapheresis normalizes compensatory protective response and contributes to the functional capacities of the majority of these patients (86.7%) due to detoxification, rheocorrective and antiinflammatory effects, while antibiotic therapy alone was ineffective (28.6%) [Sheveleva G.A. et al., 2011].

Among the causes of infertility can also note the role of pathological products and toxicants as endo- and exogenous origin. Influence of the above (see "Ecology and pregnancy") industrial gonadotropic chemicals with suppression of reproductive function, both women and men in these cases there is no doubt, as is obvious and the need for preventive courses cleansing the body before gestation.

Miscarriage 21-32% of women due to hyperandrogenism. With symptoms of hirsutism in 6 times more likely to occur early spontaneous abortions and 10 times more non-developing pregnancy [Kon'kov D.G. et al., 2008]. In such cases, apheresis therapy should also provide a more favorable course of pregnancy.

We can not exclude the role of the HLA system in the genesis of miscarriage. This system is responsible for the reaction of transplantation immunity. When HLA-incompatible women and men, and, therefore, both the mother and the fetus in women formed HLA-antibody by allo-sensitization. This is especially likely when the secondary infertility and miscarriage. Along with allo-sensitization to HLA in women also develops auto-sensitization in the form of production antilymphocyte autoantibodies belonging to the same locus HLA-identical antigens wife and husband. At the same HLA-antibodies in women lead to recurrent miscarriage and infertility. And it is clear that to bring such HLA-antibodies can also be just using plasmapheresis.

But there is another cause of infertility, which can be eliminated with apheresis therapy. We are talking about women isooimmunization spontaneous formation of spermatozoa with antibodies against their antigens [Shulman S., 1986]. In these cases, sperm activity is inhibited before fertilization of the oocyte. Sperm antibodies are found in both the blood and in the intrauterine fluid. They cause infertility by interfering with sperm motility and transport blockade on their cervical canal. They even affect the processes of implantation and embryo growth [Hirano M. et al., 1999]. Yu.A.Kotlik and
I.Yu.Kuzmina (2006) noted that spermio-immobilization test Izodzhima (Isojima) cervical mucus was positive in almost all women with immune infertility. Nevertheless, iso-sensitization to own sperm observed in men, which is also one of the reasons for the "male" infertility. Among its reasons play an important role autoimmune disorders when, after often have long forgotten injuries and even varicocele, orchitis-epididymitis arise autoantibodies against their own sperm, that found in 8-21% of cases in men for suspected "masculine" infertility. They are able to break as sperm motility and ability of the latter to penetrate the oocyte membrane, without which it is impossible even in vitro fertilization, the success of which in such cases does not exceed 40% [Vazquez-Levin M.N. et al., 1997].

In addition to the functional state of autoantibodies may affect sperm and other toxic compounds as exogenous and endogenous origin, in particular – the generation of excessive amounts of cytotoxic oxidants [Abramov Y. et al., 1998]. The content of such autoantibodies in the blood can be increased to 3000-4000 units/ml (normal 75 units/ml) and 500-2000 units/ml in the ejaculate (at the same rate) [Koren’kov D.G. et al., 2003]. Described the appearance of autoantibodies and spermatozoa in men with detected virus (HSV, CMV) infections (31.1%) or with their biocenosis of bacteria (61.4%) [Atyushev G.P., Motavkina N.S., 2006].

Just using plasmapheresis can derive such antibodies and other toxic products from the body and provide a safe environment for fertilization. Thus D.G.Koren’kov et al. (2003) noted an increase in the total number of sperm in the ejaculate by 46% and the number of motile cells by 30-123% after a course of plasmapheresis in men that in 42% of cases the wives of these patients become pregnant.

It should be noted that the presence of an autoimmune disease can be accompanied by maternal disorders of the immune and endocrine systems in the newborn. Thus, during the early neonatal adaptation they frequent have decreased level of cortisol (46%) and neonatal hypothyroidism (24%). Children may be born with elevated levels of antiphospholipid antibodies (62%) and antibodies to human choriocarcinoma. The presence of increased amounts of neonatal specific autoantibodies class M indicates also the ability of their own to the synthesis of these antibodies, that indicating a higher risk for development of their autoimmune diseases in the future [Ponomarea L.P. et al., 2001]. These data once again show the need of plasmapheresis in pregnant women in the presence of virtually any autoimmune pathology [Voinov V.A., 2013].

Obesity. Hippocrates in the IV century BC, said: "And obesity and leanness should be condemned. Uterus unable to take seed and menstruating regularly". And indeed, now proven that obese women significantly more likely to develop anovulation, polycystic ovary syndrome, amenorrhea and infertility [Borovkov E.I., 2010]. During
pregnancy in these women is more likely to occur gestational diabetes also, which poses a threat to birth defects in fetal development [Lee A.T. et al., 1999]. More frequent and more difficult runs and preeclampsia with prevalence of hypertensive forms [Ailamzyan E.K. et al., 2000]. All this makes the justified and courses of plasmapheresis in these patients [Rubtsova E.A., 2003].

It should be noted that the presence of maternal autoimmune disease can be accompanied by immune and endocrine system disorders in the newborn. Thus, during the early neonatal adaptation they frequent have hypocortisolemiya (46%) and neonatal hypothyroidism (24%). Children may be born with elevated levels of antiphospholipid antibodies (62%) and anti-human chorionic gonadotropin. The presence of increased amounts of neonatal specific autoantibodies class M also indicates of their own ability to the synthesis of these antibodies, indicating a higher risk for their development of autoimmune diseases in the future [Ponomarev L.P. et al., 2001].

**In vitro fertilization (IVF)** is used more widely, but not always comes a long-awaited pregnancy. This suggests that the presence of anatomical barriers to natural fertilization are not excluded and several other of the above factors contributing to infertility and miscarriage. There is evidence of the effectiveness of the use of plasmapheresis, even in patients with tubal- peritoneal infertility in preparation for IVF and embryo transfer into the uterus, not to mention the need for prior removal of antiphospholipid antibodies, antibodies to human chorionic gonadotropin, and other autoantibodies, as well as in the order of treatment and prevention herpes, cytomegalovirus and other infections [Ochan A.S., Fedorova T.A., 2007]. All of this should help to increase the probability of pregnancy and provide better conditions for fetal development.

**Complications of pregnancy, dangerous for the mother**

All of the above complications of pregnancy is a major cause of perinatal morbidity and mortality, although they do not always posed a serious threat to life and health of the mother. Nevertheless, a number of complications and pose is a real threat to the mother.

Dangers of drug therapy during pregnancy occur not only to the fetus, but the woman too. Such conditions include ovarian hyperstimulation syndrome, which develops in the treatment of infertility in order to increase the number of mature follicles and ovulation stimulation using anti-estrogens, and gonadotropin agonists “gonadotropin releasing hormone.” Among the most serious consequences of this syndrome describe severe endotoxemia with increased vascular permeability, hypoproteinemia, hypovolemia, hemoconcentration, leading to the appearance of
ascites, hydrothorax and hydropericardium, as well as the development of hypercoagulability and thromboembolic multiple major vessels until death. Frequency abortion this background is 29%, and premature birth – 44%. 62% of neonates are born underweight. 13% of pregnant women against this background develops hypertension, at 5.9% – pre-eclampsia, in 4.4% – gestational diabetes, 4% discontinuities of placental arise or abortion. 44% of pregnant delivered by caesarean section [Abramov Y. et al., 1998]. There are attempts to prevent the development of this syndrome by the introduction of massive doses of albumin at the time of egg retrieval or immediately after proved unsuccessful [Ndukve G. et al., 1997]. And so far the most radical method of treatment is an emergency interrupt long-awaited pregnancy.

At the same time, the use of therapeutic plasmapheresis in the development of ovarian hyperstimulation syndrome in most cases can cut its manifestations. In order to prevent this complication in preparation for in vitro fertilization and background as pregnancy and appropriate use of therapeutic plasmapheresis, able to reduce the activating effect of superovulation on the hemostatic system and create more favorable conditions for the process of implantation and subsequent development of the embryo [Ochan A..S et al. , 2007].

**Bleeding.** Prevention of bleeding remains one of the most pressing problems of obstetrics. Their frequency ranges from 2.7 to 8% of the number of labor. In pregnant by the end of III trimester of pregnancy there is a pronounced hypercoagulable by increasing the activity of clotting factors – increasing the content of fibrinogen, platelet aggregation, lowering blood fibrinolytic activity. These processes are most intense in the presence of antiphospholipid syndrome in pregnant women [Ponomarev I.V. et al., 1999; Demina T.N. et al., 2004].

Development of DIC often occurs during labor complicated by bacteremia the spread of infection from the birth canal, or with infected amniotic fluid [Graeff H et al., 1980]. Amniotic fluid embolism, even in the absence of infection, and often lead to the development of the internal DIC and profuse bleeding. This is facilitated by preeclampsia and premature detachment of the placenta, and intrauterine fetal death.

Abruptio placenta is one of the leading places in the structure of maternal and perinatal mortality. The main reason for this is premature placental abruption there is preeclampsia (51.9%), and perinatal mortality in such cases reaches about 21.9% [Zabolotnov V.A. et al., 2008].

Without going into the details of the treatment of bleeding already arisen held by all the canons of Hemostasis and Transfusion medicine, focus only on measures to prevent them.

In all cases, the main motivating factor for the occurrence of DIC and placental pathology is the accumulation of substances membranotropic with excitation platelet
aggregation, as well as disorders of the placental circulation. Therefore, all of the above methods of apheresis therapy of preeclampsia and other endotoxosis will serve as prevention and such bleeding also. Nevertheless, and at iso-coagulation, not typical for this gestation period, and the high risk of bleeding during childbirth O.V.Rogachevsky et al. (2005) for the correction of the hemostatic system is considered the method of choice a exchange plasmapheresis, which allows to significantly increase the blood coagulation potential, improve microcirculation and tissue oxygen supply. In 15 of these patients using plasma exchange (replacement of the removed plasma volume conducted by fresh frozen plasma donation 1:1) succeeded in increasing the blood coagulation potential with hypercoagulability according coagulogram and none of them bleeding during childbirth and the postpartum period was not observed.

T.N.Demina et al. (2004) during the course of therapeutic plasmapheresis in 80 pregnant women with antiphospholipid syndrome also in neither case did not observe bleeding during childbirth, while in the control group of 60 pregnant women in 4 (6.7%) had abruptio placentae, and the two developed DIC with hemorrhage 1100-1300 ml.

However, against the background of already come complications, performing therapeutic plasmapheresis prevents the onset of more severe multiple organ disorders post-hemorrhagic [Demina T.N. et al., 2004]. At the same time, plasmapheresis should begin as early as possible, as continued circulation thrombogenic factors in the bloodstream can cause repeated coagulation disorders. Plasmapheresis on a background of generalized hemorrhagic syndrome with decreased levels of prothrombin less than 50% and increased bleeding from the injection site within the first 12 hours after the onset of bleeding significantly reduces mortality [Serov V.N. et al., 2000]. It should be borne in mind that in the context of anticoagulation membrane plasmapheresis can be carried out completely without heparin using a solution of sodium citrate only.

The Thrombotic Thrombocytopenic Purpura (TTP) promotes development of severe multiple organ insufficiency against the DIC-syndrome. In such cases only plasma exchange is capable to stop such complication [Jagia M., 2013]. TTP can arise even in the first trimester of pregnancy and the plasma exchange here helps too [Jamshed S. et al., 2007; Sikka P. et al., 2013]. Plasma exchange can be combined with cryosupernatant and a platelet transfusion [Fyfe-Brown A. et al., 2013]. L. Myers (2010) emphasized that without plasma exchange TTP outcome almost always the fatal.

Eclampsia. Increase in the severity of late toxicosis (preeclampsia) before birth in some cases dictates the urgent need abortion to save the mother, regardless of the fate of the baby, as eclampsia, the maximum phase of preeclampsia, threatens toxici
brain edema (coma, convulsions, retinal detachment), toxic pulmonary edema with severe parenchymal respiratory failure, nephropathy until anuria, liver failure (steatosis, acute “yellow atrophy of the liver”). Each of these complications, not to mention their combined one-stage, threatens the life of the mother and requires the most urgent measures of intensive therapy. Thus the most reasonable pathogenetic submitted detoxification and apheresis therapy [Vetrov V.V., 2000].

Therapeutic apheresis undertaken in prenatal, provides a more favorable environment for future childbirth, and even for emergency delivery, which create additional and significant burden on the major organs and systems. In addition, we cannot exclude the possibility of prolonging pregnancy in its early timing, although it should be recognized that the fetus while already in extreme conditions of existence for quite some time and complete recovery of his health at the time of delivery is a major challenge. This emphasizes the need for timely preventive detoxification and apheresis therapy throughout pregnancy and even before it.

In the postpartum period apheresis therapy aimed at restoring health, and sometimes exclusively on resuscitation of the mother. The effectiveness of these measures depends on the time of their inception. Given the need for anticoagulation and risk cause or exacerbate bleeding, the earliest date for such procedures after delivery or cesarean section is 6 hours. The complex of these measures may conduct hemosorption, plasmapheresis, plasma exchange, plasma adsorption, ultrafiltration, photo-hemo therapy and indirect electrochemical oxidation of blood. Volume and a combination of these procedures depend on the type and degree of homeostasis disorders, organ failure. Plasmapheresis, conducted against the backdrop of preeclampsia in the postpartum period, allows to reduce the level of endotoxemia, restore diuresis, lower serum creatinine, bilirubin, transaminases, normalize coagulation [Vetrov V.V. et al., 2000; Bukin V.E., 2004; Serov V.N. et al., 2011].

Our own experience of these events shows that detoxification contributes much more rapid reconstitution of the affected organs than traditionally held therapy – medication, infusion, artificial ventilation, and even hyperbaric oxygenation. In particular, diuresis, even against complete anuria, may recover for the past hemosorption as removing "toxic press" of the kidneys, and in the next few hours there is a restoration of consciousness and of the pulmonary parenchyma.

Belated detoxification shows a delayed inverse dynamics of organ damage. However, in one case, even after four weeks of deep coma, on a background of severe parenchymatous respiratory failure and hydrops, hemosorption with ultrafiltration (2.5 L) resulted in the restoration of diuresis and elements of consciousness the next day, re hemosorption-ultrafiltration achieved full recovery of consciousness, renal function, pulmonary airiness, and only demanded more bedsores long follow-up treatment.
One of the causes of severe multiple organ failure in the postpartum period is **amniotic fluid embolism**, when in the uterus gaping vessels gets liquid containing not only urea and meconium, but also pieces of chorion. Severe toxic cerebral edema, pulmonary edema, and microemboli with disorders of the central hemodynamics and microcirculation can also be recovered using hemosorption and plasmapheresis. In our practice, when one of these cases needed also prolonged extracorporeal membrane oxygenation for 24 hours with three consecutive sessions hemosorption, which led to the complete restoration of the affected organs.

It should be noted that we used the device for membrane plasmapheresis "Hemofeniks" with plasmofilter "Rosa" Russian production of "Trackpore Technology." Small volume filling apparatus (65-70 ml) was allowed to use it even with hemodynamic instability, when the blood pressure was maintained constant infusion only sympathomimetics [Voinov V.A., 2010].

It was possible to use also in the presence of DIC and increased bleeding. Sodium citrate solution (ACD-A) prevented thrombus formation within the extracorporeal circuit, but had no effect on the coagulation system in the body, because it will not accumulate and quickly disposed of the tissues.

Portable nature of the device, automatic operation mode ensure the security of membrane plasmapheresis and away to other hospitals. It can be successfully used during plasmapheresis in an outpatient setting. An additional advantage is the possibility of hemosorption with the same set of routes as for the membrane plasmapheresis.

**Cholestatic hepatitis (Intra-hepatic cholestasis) of pregnancy** often complicates the second half of pregnancy and is accompanied by intense pruritus, intensifying at night with sleep disturbances, nausea and vomiting. The examination revealed a 5-10-fold increase in transaminase levels, 2-3-fold increase in direct bilirubin, total alkaline phosphatase, thymol indicators. 10-100 times increase in the content of bile acids (most of cholic, chenodeoxycholic less) [Castaño G. et al., 2006; Favre N. et al., 2010]. In cholestasis very often develop preeclampsia (87%), the threat of miscarriage (65%), preterm delivery (35%) with a syndrome of intrauterine fetal growth retardation (29%), chronic fetoplacental insufficiency (87%) with perinatal mortality, reaching 15 % [Lineva O.I. et al., 2000; Pusl T., Beuers U., 2007].

These disorders are resistant usual therapeutic measures and are often forced to prematurely terminate the pregnancy [Ghosh S., Chaughuri S., 2013]. It is usually recommended to accept ursodeoxycholic acid [Grand'Maison S. et al., 2014), however it helps not always. In this regard, there are indications to eliminate toxic substances through apheresis therapy.

N.V.Deryabina et al. (2003) reported the first experience of using membrane plasmapheresis courses in 30 patients with cholestasis gestation 26-35 weeks.
Decrease of pruritus was noted after the first session of plasmapheresis, improved sleep and appetite. The normalization of bilirubin, a threefold reduction in transaminase levels, a significant decrease in alkaline phosphatase and diene conjugates with normalization of antiradical activity. In all cases, a full-term pregnancy was prolonged up to date with the birth of living and healthy children.

In the control group (44), despite the use of hepatic, antioxidants and other drugs continued to increase bilirubin, transaminases and alkaline phosphatase in the blood, which was accompanied by the deepening of hypoxia and fetal malnutrition (34,1%), placental insufficiency (27,4%). This led to the premature birth or early termination of pregnancy (11,3%), weakness of patrimonial activity (27,3%) with greater frequency of cesarean section and increased risk of fetal death (2 deadborn from 44).

Positive results of treatment of cholestasis with courses of plasmapheresis have A.V.Nikolaev et al. (2005). A. Mathias et al. (2009) also consider the use of plasmapheresis justified in such cases, though at the accompanying chronic hepatitis C it isn't always possible to stop its manifestations and in such cases haemoperfusion can provide much bigger effect [Voinov V.A., 2013; Covach A.J. et al., 2014].

Acute fatty liver of pregnant - more severe pathology associated with a high risk of neonatal and maternal morbidity and mortality. It often develops and DIC with massive bleeding also. With slightly better outlook also takes frequent complication of late pregnancy HELLP-syndrome (Hemolysis, Elevated Liver enzymes, Low Platelet syndrome). In these cases often develop hemolytic anemia and thrombocytopenia with high perinatal mortality. Genesis of these complications lies in genetically related disorders free fatty acid oxidation of fetus [Ibdah J.A. et al., 1999]. However, the complex can be traced with the appearance of autoimmune disorders autoantibodies placental tissues and liver lipoprotein lowering background amount and regulatory CD4+ CD25+ T-cells [O.P. Tan’ko et al., 2006]. Given the high risk of fetal death, premature detachment of the placenta and bleeding during childbirth expedient to intensive plasmapheresis with removal of up to 50% CPV and replacement of fresh frozen plasma donation [Padden M.O., 1999; Förster J.G. et al., 2002; Eser B. et al. 2005; Malvino E. et al., 2005; Bayraktaroglu Z. et al., 2006; Iannuzzi M. et al., 2006; Nasa P. et al., 2011; Haggermont W.A. et al., 2012; Tang W. et al., 2012; Vafaemanesh J. et al., 2014]. Usually some sessions of a plasma exchange are required and at the timely beginning of such treatment the frequency of recovery reaches 94.8% [Jin F. et al., 2012]. It is emphasized that the outcome of thrombotic thrombocytopenic purpura without plasma exchange is almost always fatal [Myers L., 2010]. Y.F.Chu et al. (2012) achieved success at the combined use of a plasma exchange and hemodiafiltration.
Hemolytic uremic syndrome in the postpartum period is often accompanied by HELLP- syndrome, and also leads to a high mortality. Emergency plasma exchange, made in the first 24-49 hours after its detection can prevent an adverse outcome [Jannuzzi M. et al., 2006; Dixit S. et al., 2012].

Purulent-septic complications. The frequency of postpartum infectious complications as high as 26%. Among the reasons was high on amniotic infection (chorioamnionitis or) with infection of amniotic fluid, chorion, placenta [Novikov O.N. et al., 2000 ]. The part of obstetric sepsis of maternal mortality rate is 37-39%, mainly due to progressive damage to the major vital organs – lungs, liver and kidneys. It should be noted a significant increase in lipid peroxidation products with inhibition of antioxidant defense system in parturients with purulent complications [Dolgoshapko O.N., 2006].

Because pregnancy itself is accompanied by physiological immunosuppression, which may be exacerbated as a result of toxicity, it is possible aggravation dormant infectious processes, among which the leading role has pyelonephritis. It can, on the one hand, aggravate and deepen preeclampsia during endotoxemia, on the other hand – increase the risk of intrauterine infection of the fetus , so the fight with pyelonephritis becomes important and not the last place here should take therapeutic plasmapheresis and photo-hemo therapy [Novikov O.N . et al., 2000; Dolgoshapko O.N., 2006].

In the postpartum period in the forefront there is the risk of endometritis, which may be accompanied by sepsis and septicemia. The severity and lightning course of endometritis caused also abundant vascularization and large suction surface of the uterus endometrium. Under these conditions, only the timely removal of circulating shock -metabolites, excess inflammatory mediators and fibrinolysis products using plasmapheresis can turn the tide of the disease, reduce the time of hospital stay from 42.4 to 24.6 bed days, length of intensive care from 29.2 to 8.4 days and reduce maternal mortality from 64% (in the comparison group) to 15.6% in the group of women in childbirth, which is a comprehensive treatment was carried out in the early stages of sepsis [Dolgoshapko O.N., Chermnykh S.V., 2008]. Many authors emphasize that the apheresis therapy should be started in the first hours of septic shock.

At the first stage of treatment is most expedient hemosorbtion indirect electrochemical oxidation and ultra-violet irradiation (UVI) of blood, and then exchange plasmapheresis sessions when removed from plasma immune non-competent elements replaced native donor plasma containing immunoglobulins, antibodies, complement, opsonins capable of immediately come to grips with pathogens [Voinov V.A., 2013]. UVI of blood and plasmapheresis performed during
pregnancy about preeclampsia, reduce the risk of septic complications after cesarean section [N.F. Ivannikov et al., 2000].

V.V.Vetrov et al. (2003) reported on the experience of using hemosorption, plasmapheresis and blood UVI 124 postpartum women with postpartum infections (pyelonephritis, metro-endometritis) with good clinical effect, allowing you to reduce the dose of infusion and antibacterial agents, and their hospital stay was 3-5 days less compared with a control group of similar patients. These results allowed us to move to a preventive plasmapheresis and blood UVI 64 postpartum women at risk of developing postpartum infections. In these cases, the outcome of the post-partum period was favorable in all women with improved health, lactation, involution of the uterus, biochemical and clinical blood tests. Every fourth patient was cured without any antibiotics [Vetrov V.V. et al., 2000]. Preventive holding plasmapheresis prevents the development of multiple organ failure [Jojua T.V. et al., 2009; Meshalkina I.V., 2011].

The same tactics of apheresis therapy of septic complications and is used in gynecological practice in endometritis after illegal abortions, pelveo-peritonitis etc. In some cases, it is timely detoxification can cut acute inflammatory process and avoid hysterectomy have more young and nulliparous women. In addition, plasmapheresis can cut menstrual irregularities and uterine bleeding during chronic inflammatory diseases of the pelvic organs in girls [Nemchenko O.I. et al., 2004].

There is considered rational perform preventive apheresis therapy at the planning stage of pregnancy, which helps to improve the clinical status of patients with increasing inter-recurrent period 2.9 times, reduction in the severity of prodromal symptoms in 3 times, improving the body’s detoxification function, which should provide more favorable for future pregnancy.

**Neonatology**

As noted above, serious complications pre-, intra- and post-natal periods lead preeclampsia, accompanied by the same toxemia, followed fetal intrauterine hypoxia, aggravated its consequences exacerbations of chronic urogenital infection and rhesus-conflict mother and fetus.

These complications are the main causes of fetal death. They contribute to premature birth, in which even born alive, the baby is in critical condition with a complex multiple organ disorders, can not be corrected with the help of any artificial or assisted ventilation with oxygen or hyperbaric chambers, no antibiotics or any other medications.

This is because in the circulation, interstitium and cells of the body are found in a huge variety of toxic products that do not give way to restore normal metabolism of
organs and tissues with the development of a series of vicious circles. Toxic press makes it impossible to establish a normal hepatocytes, alveolocytes, neurons, renal parenchyma, which delays the recovery of natural detoxification processes, allocation and gas exchange. Break these vicious circles without removing of toxic products is almost impossible, which explains the significant incidence of early neonatal mortality and allegedly recovered child is doomed from childhood remain chronically ill, suffering from liver disease until cirrhosis, kidney, lung, and various manifestations of allergy and immune shifts, which differ little from the acquired immunodeficiency syndrome, ie actually AIDS. The frequency of disorders of the nervous system in newborns of their mothers with preeclampsia reaches 15%. Most often it is hypoxic and ischemic damage with subsequent disability children. This encephalopathy is a consequence of severe metabolic disorders in the brain tissue, a kind of "metabolic catastrophe" [Kulakov V.I. et al., 1998]. Perinatal cerebral hypoxia remains one of the most common causes of chronic subsequently developing neurological disorders, mental retardation and even epilepsy [Vannucci R.C., Perlman J.M., 1997].

Intrauterine growth retardation affects the subsequent growth of the child. Such children have greater incidence of mortality and morbidity with a higher frequency of cardiovascular disease, hypertension, hyperlipidemia, diabetes mellitus type 2 and other endocrine disorders, leading to their premature death as an adult [Celsi G. et al., 1998]. Although about 80% of these children in the first 6-12 months of catching up in its development of "full-length" peers, but others remain smaller growth in childhood and in adulthood, their growth is also less genetically predetermined in their families. Among the factors regulating fetal growth plays an important role, "Insulin-like growth factor," which not only stimulates the proliferation of cells of the fetus, but also affects the distribution of nutrients between the placenta and the fetus toward the latter [Cianfarani S. et al., 1998].

Attention is paid to this issue in India, where especially high incidence of diabetes type 2 and coronary heart disease in young people and in middle age that try to connect with a higher frequency of children born with low birth weight. In India, this factor is just there – the average birth weight of 2.6-2.7 kg – one of the lowest rates in the world. The examination of these children 8 years of age found that low birth weight was associated with higher blood pressure, higher levels of glucose and insulin levels after exercise testing, higher concentrations of cholesterol and LDL, greater insulin resistance. These children with low birth weight also had greater fat mass to 8 years of life [Bavdekar A. et al., 1999].

For women suffering from bronchial asthma and other autoimmune diseases is 1.5 times greater risk of having children with low birth weight. Such children are 2-3 times more likely to have allergies and obstructive pulmonary disease. Thus to 5-7 years of life half of them can form asthma [Vakhrameeva S.N. et al., 1999].
There is possible for transplacentally penetration of autoantibodies at various autoimmune diseases of mother. In particular in the presence of anti-Ro or anti-La antibodies possibly damage of fetus heart with development of a cardiomyopathy and congenital blockade of heart. In such cases plasma exchange courses at pregnant women for prevention of similar complications at children are justified [Saxena A. et al., 2014].

Naturally, such complications is easier to prevent a timely spending detoxification pregnant with the threat of intrauterine hypoxia, but after the birth of excretion of toxic products from the circulation should help more rapid and full recovery of brain and other vital organs of the newborn.

Serious problem is the meconium aspiration syndrome. Last appears in the intestines of the fetus to the 20th week of gestation, its passage in the amniotic fluid occurs for the 37th week, although pathological pregnancy find it there much earlier. If you have complications of fetal hypoxia occurs with its hyper-peristalsis bowel and easing its sphincters, which promotes the release of meconium in the amniotic fluid, on the one hand, and on the other – are excited fetal breathing movements and opening his glottis. Inhalation of meconium leads to airway obstruction, distelektasis, violations of ventilation-perfusion relationships. There are cases when meconium aspiration combined with intravascular coagulation of blood in the veins and arteries. Meconium promotes pneumonitis, hyper-inflation airway, local areas of emphysema, pneumomediastinum and pneumothorax, early septicemia, pulmonary hemorrhage and thrombosis massive pulmonary and systemic vascular microcirculation [Sergi C. et al., 1998]. Treatment of this complication is an extremely difficult problem, which once again underlines the usefulness of normal conditions of fetal development through apheresis therapy pregnant when there is suspicion of pathological course.

Often develop septic complications in newborns also. Every year they occur in 30 million infants and 1.2 million of them die [Afroso S., 2006; Zaidi A.K.M. et al., 2011]. Even in developed countries, their number reaches 520.000 and no tightening of the rules of hygiene or antibiotics are not always able to cope with them and at the same mortality as high as 40% [Blencowe H. et al., 2011].

In recent years, it appeared an increasing number of reports of such specific complications early period after birth, bronchopulmonary dysplasia as (BPD). Virtually unknown 10-20 years ago, now it is a complication of a leading place among the causes of lung diseases in children. In the United States are diagnosed each year up to 7000 such cases. Most often develops in the BPD artificially ventilated preterm infants. Mechanical ventilation and oxygen therapy increases survival of premature infants, but the risk of developing BPD is on the increase also. Underdeveloped lungs, barotrauma, and oxygen toxicity, increase in pulmonary tissue cytokines (IL-1, IL-6, IL-8), molecules "intercellular adhesion", macrophage, inflammatory proteins are the main etiological factors of complications [Singer L. et al., 1997; Thome U. et al., 1998].
BPD may develop in 20% of infants who received mechanical ventilation. Children with BPD have a higher risk of death in the early period after birth. But after discharge, these children have a higher risk of frequent respiratory diseases, growth disorders, cardiovascular disease and neurological disorders. The risk of developing BPD does not always depend on the severity of respiratory distress in newborns. Meaning of intrauterine infection is confirmed by finding fetus microbial invasion of the amniotic fluid in 25% of premature babies. It is often associated with the presence in the liquid of proinflammatory cytokines such as IL-1, TNF-α and IL-8. These microbes, cytokines and other biologically active substances can be aspirated during fetal breathing, lead to intrauterine pneumonia, making the lungs more susceptible to barotrauma and oxygen toxicity with increased risk of BPD [Yoon BH et al., 1997].

Threat to the health and even the life of the newborn alloimmune thrombocytopenia creates developing as a result of crossing the placental barrier in the event of autoantibodies mother her "gestational" thrombocytopenia. Decrease in number of platelets to her 80x10^9/l is not yet accompanied by what or clinical symptoms or even significantly increases the risk of bleeding during childbirth. However, neonatal alloimmune thrombocytopenia can lead to serious complications in the newborn, especially in disorders of childbirth fraught with intracranial hemorrhages. For the prevention of neonatal bleeding even attempted intrauterine platelets transfusions [Greaves M. et al., 1997]. Although, of course, more rational in such cases it would plasmapheresis in a pregnant that can suspected such autoimmune thrombocytopenia.

One of the serious complications at newborns, especially prematurely born, are damages of lungs – the **respiratory distress syndrome** (RDS) developing not so much owing to immaturity of surfactant system of lungs, how many because of toxic damage of lungs on the RDS adult type. It occurs owing to a severe endotoxicosis of newborns at a number of complications of a course of pregnancy of their mothers – a preeclampsia, pre-natal infections, autoimmune frustration of pregnant women which lead to premature birth. It is confirmed also by the researches performed in the St. Petersburg Pediatric medical academy [Evtukhov G. M., Ivanov D. O., 2005].

However, problems exist motility disorders and surfactant for respiratory distress syndrome in adults with acute pneumonia, "shock lung," after developing severe injuries, burns, septic complications.

**Surfactant**, reducing the surface tension in the alveoli, and thus ensuring their stability in the exhalation and reduces the hydrostatic pressure in the pulmonary capillaries, preventing the extravasation of fluid from them. Thus, the lack of surfactant leads to both atelectasis and pulmonary edema. The main active principle of a surfactant is phospholipid dipalmitoil-phosphatidyl-choline, but also exist protein
components thereof, i.e., the surfactant is a lipoprotein synthesis that occurs in type II alveolocytes.

There are several attempts to explain the decrease in the activity of surfactant. In particular, it is believed that the protein and the liquid entering the alveolus at edema, disrupt the surfactant layer, wash out it. However, possible and direct inhibition of surfactant under the influence of some toxic substances, among which are the free fatty acids [Günther A. et al., 2001; Zasadzinski J.A. et al., 2010; Lu K.W. et al., 2011]. Histochemical studies have shown that as early as 2 hours after the start of hemorrhagic shock there occur changes surfactant film alveoli, its fragmentation. Experiments on animals have also been shown to suppress the activity of the surfactant after the administration of bacterial endotoxin [Davidson K.G. et al., 2002].

We have carried out our own investigation of violations of surfactant activity, based on the methodology J.A.Clements (1957). To 3 g of lung tissue minced with scissors and extracted surfactant in 50 ml isotonic sodium chloride solution. After 30 minutes of exposure with constant agitation extract was placed in a special cell with a fortified movable barrier. The area of the cell smoothly or tiers could be reduced from 100 to 20%, making it possible to record the hysteresis loop of the surface tension, which was measured by a quartz plate retracting force on the balance of Wilhelmy - Longmyur. It was the most informative while reducing the surface tension of the cell area to 20% (corresponding to the expiration of the lungs), reflecting the highest possible activity of surfactant in the extract or "minimal surface tension." In describing the results of studies, the term "surface tension" is meant "the minimum surface tension", expressed in dyne/cm (mN/m).

Surfactant activity was determined by measuring the surface tension of lung extracts obtained from adult patients who died with symptoms of RDS on the basis of acute pneumonia and infectious lung destruction.

Activity rate for surfactant surface tension took similar pieces of lung tissue of 20 healthy dogs that under intratracheal anesthesia, a thoracotomy was performed and the subsequent experiments, unrelated to the current tasks, with subsequent excretion of their experience.

To elucidate the causes of impaired surfactant activity that was excluded influence the whole organism were special experiments in vitro, when to the lung extracts of the of dogs were added to 10 ml of blood from healthy dogs (5) healthy volunteers (5) and 10 patients suffering from RDS, pneumonia, abscess or gangrene of the lungs.

Surface tension of lung extracts of healthy dogs were on average 5.2±0.7 dynes/cm, while in patients it was 20.29±1.6 dynes/cm. In in vitro experiments, was originally established the absence of any inhibitory effect on the activity of the surfactant from blood of healthy animals and humans (blood donors). At the same time, the addition of blood of sick people surfactant activity significantly inhibited (Table 1).
Table 1.
The activity of the surfactant added to the extract after the healthy lung blood of healthy animals, healthy volunteers and patients

<table>
<thead>
<tr>
<th>№</th>
<th>Object of research</th>
<th>Initial level</th>
<th>After blood addition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Healthy dogs</td>
<td>5.2±0.5</td>
<td>5.7±1.1</td>
</tr>
<tr>
<td>2</td>
<td>Healthy volunteers</td>
<td>4.9±0.7</td>
<td>5.4±0.9</td>
</tr>
<tr>
<td>3</td>
<td>Patients with RDS</td>
<td>5.2±0.7</td>
<td>25.08±3.76*</td>
</tr>
</tbody>
</table>

Note: marked with * reliability of differences from baseline (P < 0.05).

Possibility of direct inhibition of surfactant some substances circulating in the blood, at first glance it may seem unlikely, since the surfactant lining the alveoli inside, protected from the effects of these substances alveolar-capillary membrane. However, with the development of acute lung injury permeability of the membrane is broken, and that allows it to penetrate into the alveolus with edematous fluid and thus toxic substances. In this case, it is possible direct contact with surfactant.

Thus, research has convinced us that the pathogenesis of acute lung lesions surfactant system disorders have secondary role, being not so much the cause as a consequence of these lesions.

In connection with the development of methods for the production of synthetic or semi-synthetic surfactants increased interest in the possibility of their use in the treatment of RDS [Yakovlev V.N. et al., 2011]. Nevertheless, A.Anzueto et al. (1996) when analyzing the results of a large randomized trial of surfactant therapy in 700 patients did not reveal any effect on the incidence or survival, duration of mechanical ventilation and stay in ICU, or condition of physiological functions of the lungs. Many later studies have also noted a short-term effect of administration of exogenous surfactant [Spragg R.G. et al., 2004; Davidson W.J. et al., 2006; Bream-Rouwenhorst H.R. et al., 2008; Kesecioglu J., Briel M. et al., 2010; Matthay M.A., Zemans R.L., 2011]. In particular, A.V.Vlasenko et al. (2006) noted that the use of surfactant helps reduce duration of mechanical ventilation and length of stay in the ICU, but a significant decrease in mortality has not occurred (causes of deaths were sepsis and multiple organ failure). And the use of surfactant in infants provided more rapid decline in FiO₂ to 40% and reducing the duration of mechanical ventilation, but to increase survival to 7 and 28 days was also not achieved [V.Y. Shalamov et al., 1999].

This is understandable, since our studies described above have shown that surfactant is destroyed due to the penetration into the alveolus of circulating toxic products. Therefore, no matter how much of surfactant added to the lungs, but if you
do not remove toxic substances from the blood, the newly introduced surfactant will be just as well to break down, as theirs own.

Thus, no satisfactory results of use of surfactant, on the one hand, and achieving much better results in the application of methods of detoxification for RDS, on the other hand, suggests that the true cause of the fall of surfactant activity is its inhibition of toxic substances penetrating into the alveolus at toxic violation of vascular permeability. Thus introduced exogenous surfactant, as well as natural and falls under the effect of these toxic substances, and their activity ceases.

Using detoxification contributes to the elimination of porosity vascular is more reasonable pathogenetic treatment of RDS, as after the termination proceeds into the alveolus of toxic substances in the coming hours restored reproduction of natural surfactant, which eliminates the need for its introduction of exogenous drugs.

This also applies to cases of **RDS in premature infants** who do have a deficiency of surfactant, but most often develops on RDS "adult" type – as **toxic pulmonary edema** as a result of entering the bloodstream of the fetus when the mother endotoxins disorders of pregnancy, which caused a premature birth. This occurs due to severe neonatal endotoxemia in a wide range of complications during pregnancy their mothers – preeclampsia, intrauterine infections, autoimmune disorders, pregnancy, which lead to premature birth. This is confirmed by studies in St. Petersburg Pediatric Medical Academy [Evtyukov G.M., Ivanov D.O., 2005].

You should consider a limited use of exogenous surfactants, since in the presence of toxic pulmonary edema penetrate the alveoli also products that inhibit not only natural, but also input from outside surfactant that practically negates the effectiveness of such therapy. Without excluding the possibility of its implementation, it seems to us that the first thing you want to stop delivery of such inhibitors of surfactant in the alveoli by reducing the permeability of the vascular endothelium, achieved detoxification using plasmapheresis. In such cases may not require use of exogenous surfactant, since the normalization of metabolism of the lung parenchyma, including type II in alveolocytes, reproduction of necessary surfactant amount is reached in a few hours. This was confirmed by our own experience of plasmapheresis in very preterm infants, when X-ray examination a day after such a procedure is almost restored pulmonary airiness, gas exchange and the normalization of their functions. Therefore, such a newborn justified the use of detoxification – specially developed the one-needle method syringe membrane plasmapheresis with Plasmofilter PFM [Voinov V.A. et al., 1996], after which there is no need in the additional introduction of exogenous surfactant.

The most surprising was the restoration of the airiness of the lung fields X-ray examination the next day after syringe plasmapheresis, which would be difficult to expect while providing an artificial ventilation and traditional drug therapy.
All the above facts indicate the vital need for emergency normalization of the internal environment of newborns.

In this method a syringe membrane plasmapheresis made it possible to carry out the apheresis therapy of newborns, including premature weighing from 700 g also. Indications were complicated intrauterine infection, septic complications, consequences of severe asphyxia, hyperbilirubinemia soil hemolytic disease of the newborn [Polyakov S.Z. et al., 1995]. M.A.Vyugov et al. (2003) reported a significantly more pronounced decrease in the dynamics of bilirubin at hemolytic disease of 23 newborns after they undergone syringe membrane plasmapheresis. Syringe method plasmapheresis also been successfully used in the treatment of 33 babies with the syndrome of endogenous intoxication, hemolytic disease (29) and septic complications (4) [Zauralskiy R.V. et al., 2004]. The same results in the treatment of hyperbilirubinemia in neonates using membrane plasmapheresis were achieved Yu.A.Batman et al. (2009) in Donetsk (Ukraine).

Given the severity of the babies with significant disorders of circulatory dynamics and gas exchange, plasmapheresis operation required careful to maintain the constancy of the BCV and general body hydration. Plasmapheresis was carried out in a synchronous plasma exchange to the completion of an equal volume of plasma removed by donor fresh frozen plasma or native with replacement 1-2 PCV, which led to a significant decrease in the degree of endotoxemia with the normalization of clinical and laboratory parameters. This ensured a reduction of time spent in the ICU by 25% in generalized infections and septic complications and 6.7% with severe asphyxia. Mortality in these groups was decreased by 35.3% and 5.7%, respectively. And decreased time finding children on mechanical ventilation, need sympathomimetics infusion, enteral nutrition [Polyakov S.Z. et al., 1995]. Positive results using plasmapheresis in purulent-septic diseases of newborns were obtained by other authors [Mirlas M.F. et al., 2005].

Admittedly that timely membrane plasmapheresis babies in critical condition can be rather efficient way to prevent and above bronchopulmonary dysplasia and other complications detected at a later stage of the development of children.

It should be noted that indications for apheresis therapy should occur not only in critical conditions, but when the immediate threat to life of the newborn is not. Transferred endotoxemia and intrauterine hypoxia, especially in prematurity when the causes of preterm birth is the phenomenon of preeclampsia or intrauterine infection, undoubtedly accompanied by significant violations of the internal environment. Only removal of pathological products from the body can create conditions for full recovery of most of the functions, correct structural tissue disorders, metabolism and immunogenesis. Essentially, each premature baby has significant disorders of homeostasis, because the very fact of premature birth involves a complicated
pregnancy with the accumulation in the body, both the mother and fetus of a number of pathological metabolites. In these cases, it may well go about preventive apheresis therapy, in which also is plasmapheresis. Removing pathological products of the internal environment of a premature baby can be "lifted" from his "dark and musty basement ” on the mezzanine light and thus create a higher starting level for its further development and life.

But even more justified is timely carrying out a plasma exchange at emergence of the complications of pregnancy described above and then all questions of ensuring intensive therapy of newborns will be removed. They will be born in time and obviously healthy.

**Conclusion**

Thus, these data suggest an important role of disorders of the internal environment in the genesis of many of the complications of pregnancy, leading to impaired fetal growth, premature birth and miscarriage, perinatal and maternal mortality. While removal of toxic metabolites and autoantibodies using apheresis therapy is much more effective than drug therapy [Voinov V.A., 2012]. Affordable and safe method of apheresis therapy for pregnant women and newborns, is membrane plasmapheresis.

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