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Article name: **Влияние СКЭНАР-терапии на течение беременности, родов, состояние новорожденного и ребенка первого года жизни у женщин с невынашиванием беременности инфекционного генеза**

Influence of SCENAR-therapy on the pregnancy course, labor, state of a neonate and a first-year child in women with miscarriage of infectious genesis

Abstract: We investigated effectiveness of SCENAR-therapy in complex treatment of 60 pregnant women with urogenital infections at 16–18 weeks of pregnancy. The control group included 50 pregnant women with similar urogenital infections that underwent conventional antibacterial and antiviral therapy after 16–18 weeks of pregnancy. Using SCENAR-therapy in treating pregnant women with miscarriage of infectious genesis significantly improves prognosis of bearing a child, the state of a fetus, neonate and a first-year child, decreased the incidence and severity of placental inflammatory processes and intrauterine infection.

Miscarriage is not only current medical concern, but also a serious social-economic problem with the case rate 15-20% among all desirable pregnancies. Today urogenital infection is one of the major causes of miscarriage, which may have harmful effect on the course of the pregnancy, state of a fetus and a neonate. Infectious pathology is mainly caused by genital microplasmas, clamidia, herpes simplex virus (HSV) and cytomegalovirus (CMV) [5, 7, 12].

New conditions for infection development are created during gestation. It is connected with general and local immunity peculiarities of pregnant women. Systemic gestational immunosuppression (suppression of inflammatory TH-1-immune response route) in healthy women provides formation of immune tolerance to semiallogenic fetus and pregnancy bearing.

During development of acute urogenital infection or reactivation of chronic urogenital infection the T-helpers in the pregnant body significantly decrease and that activates local and general cytotoxic immune, as well as causes depression of humoral Th-2-immune response route. Infectious agents cause hypersynthesis of anti-inflammatory cytotoxicants (TNF, interleukin-1) providing prothrombinase overproduction, activation of coagulation mechanisms, thrombosis in trophoblast vessels, destruction of vascular endothelial and trophoblast damage, as well as production of antiphospholipid and anti-DNA antibodies and formation of specific cytotoxic immune response directed against fetus antigens. Hyper amount of Th-1-route cytotoxins increases the production of prostaglandin in amnion and decidua and may cause abortion [7, 11, 12, 14, 15].

It is proved that even massive virus and bacterial infections may not influence the course of pregnancy and fetus development in case a pregnant woman has no evident changes in the immunity. So, negative effect any infection has on a fetus and a neonate mainly depends on the intensity and character of immune status changes of a pregnant woman [12].

Infectious agents may cause certain complications in the course of the pregnancy: abortion (31.7-67.5%), early gestosis (32.4%), gestosis (23.7-49%), pyelonephritis (7-21.4%), anemia (92%), production of autoimmune antibodies (19-51.1%), fetoplacental insufficiency progression (47.6-73.3%), and preterm labor (8.8-16%). Women with urogenital infections may have the following complications during the childbirth: preterm amniorrhea (27.7-39%), pathological preliminary period (6.6-7.1%), labor anomaly (7.1-38.5%). In all types of infection afterbirth period is complicated by subtle late-onset (5-7 days after labor) endometritis (8.4-21.4%) with relapses and uterus subinvolution (13.5%) [5, 12].

It is known that placenta and embryonic membranes protect the fetus from bacteria and viruses. In most cases infectious process just affects placenta and starts the development of adaptative reactions in it (increase in villi vascularization, formation of syncytial node, villi proliferation with increase in placenta volume and mass). At this a newborn can be healthy with good physical and functional parameters. If the effect of infectious activator is too long or repeated, placental porosity excoriates causing the development of placental insufficiency and infectious process in the fetus. Literature says that when bacterial and virus infection inflammatory changes in placenta occur in 11-78.4% cases, placental insufficiency – 50-60%., intrauterine infection develops in 6-53% cases. High incidence rate of fetus infection was observed when inflammation of placenta fetus part and umbilical cord are combined, as well as in virus-virus or virus-bacterial associations. 36.8% of neonates born of women

with placental infectious changes have infectious diseases, 25% - hypoxic syndrome and increase of the adaptation period, 55.7% - late cord remain rejection [8, 11, 12, 16, 17, 19].

Intrauterine infection by micoplasmas is observed in 35%, by ureaplasmas – 45%, manifestations of micoureaplastic fetus infection are aspiration syndrome, interstitial pneumonia, cardiopathy. The most common infections among neonates are: meningitis, encephalitis, skin necrosis, conjunctivitis, pneumonia, osteomyelitis, hemorrhagic syndrome. Intrauterine infection by clamidia is observed in 9.7-63.3% and manifests in a generalized form (affection of eyes, kidneys, skin, lymph nodes), meningoencephalitis, gastroenteropathy, intrauterine pneumonia, conjunctivitis and vulvovaginitis in girls. Intrauterine infection in cytomegalovirus is observed in 0.2-40%, in herpetic infection – 0.01-75%. In most cases fetus infection is connected with primary virus infection during pregnancy. The fetus may be infected transplacental or while passing through the infected maternal passages. In cytomegalovirus the neonate can get infection through the infected breast milk. In cytomegalovirus the fetus has hydrocephaly, hydronephrosis, cystic changes in organs and tissues, as well as hepatitis, nephritis, encephalitis, myocarditis; neonates have the neonatal disease developing (low-birth-weight, jaundice, hepatosplenomegaly, pneumonia, meningoencephalitis, chorioretinitis, interstitial nephritis), developmental defects (microcephaly, paraventricular cyst, biliary atresia, multicystic kidneys, heart failure), late complications (deafness, blindness, encephalopathy, pneumosclerosis, cirrhosis, bowel and kidneys affection, etc). Herpes infection mainly affects the central nervous system, skin and mucous of a fetus, generalized form is also possible; congenital syndrome is observed in neonate (microcephaly, chorioretinitis, intracranial calcification) [5, 6, 9, 10, 12, 13].

If a fetus is infected but there are no manifestations of intrauterine infection, a neonate will have CNS (75-84%), CVS and GIT (26%) dysfunctions. Such children have high risk of developing infectious and allergic diseases, as well as psychomotor retardation during the first year of their life [12].

Modern complex antibacterial and immunocorrective therapy for pregnant women with urogenital infections doesn't protect from intrauterine infection of the fetus, development of fetoplacental insufficiency, thrombophilic complications, labor anomaly, as well as doesn't improve perinatal outcomes. These are the reasons why doctors still search for new therapies for treating miscarriage of infectious genesis. In different publications we can find discussions on how urogenital infections influence the course of pregnancy and there are contrary points of view on whether pregnant women with urogenital infections should undergo immunocorrection or not. That is why we found it logical to study the effect of infections on the course of the pregnancy, labor, state of a neonate and 1-year child after pregnant women underwent traditional treatment, as well as complex therapy including SCENAR-therapy.

SCENAR is used for therapeutic non-invasive electropulse stimulation of the skin in different pathologies. Pulse bipolar alternate current is used as a stimulating signal sent as pulses with the frequency 10-350Hz including swinging frequency mode (30-120Hz) and can be combined into bursts (2-8 pulses) with repetition rate 540Hz-4.5kHz [18].

Previous researches of Nizhny Novgorod State Medical Academy [1-3] show that SCENAR-therapy has immunomodulatory and anti-inflammatory effect produced due to the decrease of anti-inflammatory cytokine levels. It also normalizes coagulate blood properties due to the decrease of thrombocyte ADP-aggregation and fibrinogen content, as well as antibody levels to cardiolipins, chronic gonadotropin and DNA.

The experiment with white mongrel rats showed that SCENAR short-pulse signals lack embryotoxic and teratogenic properties [4], and that allows to use SCENAR-therapy for treating pregnant women.

Using SCENAR-therapy for treating pregnant women is allowed upon authorization of local ethic committee under State Health Care Institution Nizniy Novgorod Regional Clinical Hospital named after N.A. Semashko. All the women gave a written consent for undergoing SCENAR-therapy.

Research aim was to compare the course of pregnancy, labor process, the state of a neonate and a first-year child of women with miscarriage of infectious genesis while treating urogenital infections with traditional therapies, as well as complex therapy including SCENAR-treatment.

Materials and methods

110 women with urogenital infections composed a control group. All the women were examined, observed clinically during pregnancy, as well as during the childbirth. We also examined the state of the fetus and a neonate.

All the patients were examined at 10-12, 22-24, 36-38 weeks of pregnancy for any manifestations of urogenital infections (chlamydiosis, mycoplasmosis, ureaplasmosis, cytomegalovirus and herpetic infections). To diagnose micoplasmosis and ureaplasmosis we used bacteriological test – inoculation of cervical canal. To find chlamydiosis, cytomegalovirus and herpetic infections we examined separate cervical canal using the method of polymerase chain reaction (PCR) and blood serum for antibodies (immunoglobulin class A, M, G) to the abovementioned infections using enzyme immunoassay.

In the postnatal period we studied morphological picture of 30 placentas, all the neonates underwent saliva and tear PCR-diagnostics, as well as cord blood EIA to find urogenital infections. First-year children were followed up by neuropathologist.

All the women we observed had urogenital infections as mono-infections (34.5%) or bacterial-virus associations (65.5%). Patients were divided into 2 groups considering their age, social status, past

gynecological and extragenital diseases. Patients from the control group (50 women) underwent traditional antibacterial and antiviral therapy after 16-18 weeks of pregnancy. While patients from the main group (60 women) after 16-18 weeks of pregnancy underwent complex therapy with SCENAR-stimulation for 10 days according to the common method, including stimulation of cervical area, vertebral and paravertebral lines, 6 points, liver projection area.

The results were processed using application package for static Excel data processing and accurate difference between the indices was estimated according to the Student's test. Difference between the compared values were considered as accurate when $p < 0.05$.

Research results and discussion

When comparing clinical picture of the pregnancy we got accurate difference between the indices in main and control groups. So, in control group threatening miscarriage in the I and II pregnancy stages and threatened premature labor were registered in 26%, fetoplacental insufficiency – 20%, arrested fetus prenatal development of the I stage – 8%, dysfunction of utero-placental blood flow of the I stage – 10%. While in the main group miscarriage and fetoplacental insufficiency reduced twice. Acute infections (mainly micoplasmic-herpic and chlamidial-micoplasmic-cytomegalovirus) were observed in 31 (62%) women from the control group, where 10 (20%) had recurrent infection at 36-38 weeks, and in main group process reactivation was observed only in 11 (18.3%) cases and only at 20-24 weeks of pregnancy.

Accurate difference between the indices of the control groups was also manifested while analyzing the labor process. In the control group 44 (88%) women had spontaneous labor, 39 (78%) had labor in time, 5 (10%) – premature labor, 6 (12%) – cesarean section at 38-40 weeks. In the main group 55 (91.7%) women had labor in time and 5 (8.3%) - cesarean section at 38-40 weeks. In the control group 80% had xerotocia, compared to 60% in the main group, primary uterine inertia was observed in 30% and 20%, oxytocia – in 10% and 6.7% respectively. No complications observed in the afterbirth period in both groups. Clinical picture complications of the pregnancy and labor in women with miscarriage of infectious genesis are shown in the table.

The results presented in the table show that complications in the course of pregnancy and labor in women with miscarriage of infectious genesis in both (main and control) groups were observed mainly in the mixed bacterial-virus infection. Estimating the labor outcome for the fetus and the course of neonatal period we found out that in the control group neonates weighted $3206.6 \pm 154.7g$, while in the main group the weight was $3280.6 \pm 176.4g$. 5 neonates from the control group (10%) were born premature, 34 (68%) were born with a satisfactory state (8-10 Apgar scores), 9 (18%) – with light asphyxia neonatorum, 7 (14%) – with moderate asphyxia. Influence of SCENAR-therapy on the pregnancy course, labor, state of a neonate and a first-year child in women with miscarriage of infectious genesis

neonatorum and I degree hypertrophy, 16 (32%) – with adaptation disorders in the early neonatal period. In the main group the state of the neonates was much better: the state of 52 (86.7%) was estimated as 8-10 Apgar scores and only 8 (13.3%) had light asphyxia neonatorum and signs of adaptation disorders in the early neonatal period.

Complications in the course of pregnancy and labor	Control group		Main group	
	mono-infections	bacterial-virus associations	mono-infections	bacterial-virus associations
Threatened miscarriage	3	10	2	5
Intrauterine growth retardation	0	4	0	0
Dysfunction of utero-placental blood flow of the I stage	0	5	0	0
Placenta premature ripening	0	4	0	4
Oligoamnios	0	2	0	3
Hydramnios	0	2	1	1
Preterm amniorrhea	13	27	10	26
Uterine inertia	5	10	3	9
Oxytocia	0	5	0	4
Preterm labor	0	5	0	0

Table. Complications in the course of pregnancy and labor in women with miscarriage of infectious genesis

Examination of placenta showed some peculiarities in its morphological structure, which depend on the type of urogenital infection and its therapies. Placenta histodiagnosis in the women from the main group showed no inflammatory changes in 9 (60%) cases (women with isolated micoplasmic or ureaplasmic, micoplasmic-ureoplasmic, chlamydial, chlamydial-herpic, micoplasmic-herpic infection). Only in 4 (26.7%) placentas (in chlamydial-cytomegaloviral, chlamydial-micoplasmic infection) we found out few small inflammation focuses in fetal membranes that localized within compact layer and cytotrophoblast, not reaching amniotic epithelium, and in basal membrane. In 2 (13.3%) cases (in women with chlamydial-cytomegaloviral, chlamydial-micoplasmic-cytomegaloviral infection) we manifested single small inflammatory infiltrates in fetal membranes including amniotic epithelium layer and subchorial space and in basal membrane.

Unfortunately only 2 (13.3%) patients (treated for ureaplasmos) from the control group had no inflammatory processes. 1 (6.7%) patient had single small inflammatory focuses in fetal membranes without any damages of amniotic epithelium and in basal membrane (observed after treating isolated micoplasmic infection). 2 (13.3%) patients had changes as small inflammatory infiltrates in fetal membranes, subchorial space and basal membrane. Most often these changes were observed after treating micoplasmic (ureaplasmic) infection. Examination of 10 (66.7%)

placentas showed extensive inflammatory changes of the basal membrane, villi, intervillous lacuna, fetal membranes and subchorial space. 7 (46.7%) women out of them (mainly with chlamydial, herpic, chlamydial-herpic infections) had signs of relative compensated chronic placental insufficiency (according to the morphological diagnosis criteria of Tsinzerling and co-authors, 1998) with ill-defined focal involutive-dystrophic processes (focal dystrophic changes in syncytiotrophoblast, fibrinoid accumulation in intervillous lacuna) and well-marked adaptive reactions (hyperplasia and hypervascularization of terminal villi, enlargement of cyncytial nodes and syncytiocapillary membranes). In 3 (20%) women (with chlamydial-cytomegaloviral, chlamydial-micoplasmic-cytomegaloviral, chlamydial-micoplasmic infection) we observed signs of relative subcompensated chronic placental insufficiency with focal disorders in villi maturation (presence of embryonal, mature and immarure intervilli), diffusive fibrinoid accumulation, focal bleeding in intervillous space and active adaptive processes. So, in the main group inflammatory changes in the placentas developed after treating mixed bacterial-viral associations, had focal character and were observed 2.2 times less frequently compared to the control group, where inflammatory processes were well-marked, extensive and developed after treating both isolated and mixed infections. Moreover, the results showed that the most evident and well-marked changes in both groups were observed in mixed bacterial-virus infections.

Diagnosing bacterial and virus infections of the neonates showed that 34 (68%) in the control group) and 52 (86.7%) in the main group) children born in women both with isolated and mixed bacterial-virus infections had no bacterial and virus agents in their saliva and tear. Their blood serum contained specific IgG antibodies against infectious agents in the titer equal or twice smaller than the titer of corresponding mother antibodies. Literature says that signs not fetal infection, but placental antibody transmission [12, 20]. No specific IgM registered.

Analyzing the research results we found out that 16 (32%) neonates from the control group probably had fetal infection: in 9 (8%) neonates born in women that had acute chlamydial-cytomegaloviral, chlamydial-micoplasmic, micoplasmic-herpic infection at 20-24 week of pregnancy, IgG titer against chlamidiae, cytomegalovirus and hepic virus was twice higher than level of mother antibodies (that can sign fetal infection). No IgM found. Examining saliva and tear showed no bacterial and virus agents. Blood serum of 7 (14%) neonates, born in women that had reactivation of chlamydial-micoplasmic, chlamydial-micoplasmic-cytomegaloviral infections at 20-34 weeks and 36-38 weeks of pregnancy, contained high levels of specific IgM antibodies against chlamidiae and cytomegalovirus, titer of IgG against the infections mentioned was 2-4 times higher than the titer of mother antibodies. Examining saliva and tear showed no bacterial and virus agents.

In the main group signs of fetal infection were observed only in 8 (13.3%) neonates born in women that had acute chlamydial-micoplasmic-cytomegaloviral, micoplasmic-herpetic infection at 20-24 weeks of pregnancy. The titer of IgG antibodies against cytomegalovirus and simple herpes in these neonates was twice higher than the level of mother antibodies (that can sign fetal infection). IgG antibodies against chlamidiae was twice lower than titer of mother antibodies. No IgM found. Examining saliva and tear showed no bacterial and virus agents.

Observing the neuropsychic state of the 1-year child we found out that 34 (68%) children from the control group had normal psychomotor development. At this 16 (32%) neonates with light or moderate asphyxia born of women with chlamydial-micoplasmic-cytomegaloviral, micoplasmic-herpetic, chlamydial-micoplasmic, chlamydial-cytomegaloviral infections, extensive inflammatory changes of the fetus with signs of placental inefficiency, were observed at neurologist on perinatal encephalopathy and hypertension jitteriness (10, or 20% cases) and with psychomotor and preverbal retardation (6 or 12% cases). After they underwent treatment manifestations of perinatal encephalopathy by the end of the 1-year disappeared in 9 (8%) and remained in 7 (14%) children, whose mothers suffered from chlamydial-micoplasmic, chlamydial-micoplasmic-cytomegaloviral infections and had extensive inflammatory processes in placenta with signs of subcompensated placental inefficiency. In the main group 52 (86.7%) children had no neuropsychic disorders and only 8 (13.3%) neonates with light asphyxia born of women with chlamydial-micoplasmic-cytomegaloviral, micoplasmic-herpetic infections with ill-defined inflammatory changes of the placenta as focal chorioamnionitis and basal deciduitis had suffered from perinatal encephalopathy and hypertension jitteriness, treating which helped to relieve the symptoms and remove them by the end of the 1 year. So, in the main group the development of perinatal encephalopathy in 1-year children in mixed bacterial-virus infection of the mother was observed 2.4 times less frequently than in the control group. Moreover, in the main group by the end of the first year this pathology had been almost cured (compared to the control group).

Conclusions

1. Most often threatened miscarriage, development of fetoplacental insufficiency, labor anomaly, afterbirth pathology, intrauterine infection, neuropsychological abnormalities in the 1-year children were observed in patients with mixed bacterial-virus associations (compared to monoinfections).
2. SCENAR-therapy in pregnant women with miscarriage of infectious genesis significantly contributed to decrease the case rate and severity level of inflammatory processes in the placenta (from 86.7% cases with well-marked changes in the control group to 40% with ill-defined signs of infection in the main group).

3. SCENAR-therapy in treating pregnant women with miscarriage of infectious genesis significantly improves the prognosis of bearing a child, the state of a fetus, neonate, and first-year child, decreased the incidence of intrauterine infection neuropsychological abnormalities in the 1-year children.

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