

MODERN METHODS OF TREATMENT OF ACUTE RESPIRATORY INFECTIONS IN PREGNANT WOMEN.

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Abstract. At present, the attention of specialists is drawn to a new highly pathogenic strain of influenza A (H1N1) 2009, first isolated from cases in late March-April 2009 in California and Mexico, the spread of which led to a pandemic, which was announced by WHO on June 12, 2009.

The aim of the study. Conduct a randomized cohort study of therapies for pregnant women with acute respiratory infections.

Materials and research methods. To achieve this goal, 45 pregnant women were examined. Pregnant women were included in the examination at 12 weeks of gestation. All patients signed written consent to participate in the experiment. Of the total number of examined 22 pregnant women who did not have somatic pathology made up a comparative group. 23 pregnant women suffered influenza of varying severity in the I-II trimesters of pregnancy. The diagnosis of highly pathogenic influenza A H1N1 was confirmed by virologic testing. Of the 23 pregnant women, the main group consisted of 14 pregnant women who were treated with Viferon - the main group and 9 pregnant women who were treated with symptomatic therapy.

Research results. However, in 43% of women, ARVI symptoms developed gradually over several days, which was the reason for the later admission of patients to the hospital and was often associated with the development of bacterial complications in the form of sinusitis, otitis media, acute community-acquired pneumonia or complications during pregnancy (threat of termination) ... From the analysis of the case histories, it was found that from the moment the first symptoms of acute respiratory viral infections appeared to hospitalization, it took from 2 to 7 days, on average 3.8 ± 1.2 days. In the 1st group of patients, antiviral therapy was prescribed from the first day of admission to the hospital. The effectiveness of treatment was assessed by the duration of clinical symptoms of the disease, the development of complications and pregnancy outcomes. Typical manifestations of ARVI in pregnant women upon admission to the hospital were: rhinitis - in 82% of patients, cough - in 64.2% of pregnant women, sore throat - in 57.1% of women. Dyspeptic manifestations in the form of nausea, vomiting, diarrhea occurred in 5.2% of patients. Intoxication symptoms in the form of weakness, chills, headache were recorded in 86% (20 women).

Conclusions: Thus, the studies carried out have shown that functional changes developing in the body of a pregnant woman with moderate and severe influenza are a background for a complicated course of pregnancy and the postpartum period.

Keywords: flu; acute respiratory viral infections; viferon; Apgar scale; pregnant

Relevance. Despite significant progress in the field of prevention and treatment, acute respiratory viral infections (ARVI) today remain the most widespread human diseases, and are considered one of the main causes of reproductive losses. On the one hand, the infectious agent has a direct damaging effect on the fetus, on the other, it causes significant changes in the immune status of the mother's body, and can contribute to the development of complications of pregnancy and childbirth.

At present, the attention of specialists is drawn to a new highly pathogenic strain of the influenza A (H1N1) 2009 virus, first isolated from patients at the end of March-April 2009 in California and Mexico, the spread of which led to a pandemic, which was announced by WHO on June 12, 2009. The causative agent of influenza circulating in 2009–2010. with a high frequency belongs to type A (H1N1) California / 07/2009, it is characterized by a higher contagiousness in comparison with seasonal variants of the disease [1-7]. According to WHO, the mortality rate in influenza A (H1N1) is extremely high, for example, on the American continent it ranged from 1.6 to 9%, and in post-influenza pneumonia, the mortality rate in pregnant women was up to 17%. It is known that the sensitivity and susceptibility of pregnant women to infectious diseases are increased, they more often have severe and complicated forms of the disease. The diaphragm raised by the pregnant uterus limits the excursion of the lungs, creating an additional load on the cardiovascular system and contributing to a decrease in the severity of ventilation processes in the bronchi, a slight decrease in the respiratory surface of the lungs [8-13]. These changes make the airways more vulnerable to disease development. The woman's immune system during pregnancy adapts and acquires tolerance towards a genetically foreign fetus. How this adaptation occurs is not completely unclear, it is assumed that there is a change in the work of the immune system, which is characterized by the predominance of humoral immunity over cellular immunity. However, changes in the immune status of a pregnant woman's body lead to a certain decrease in the level of antiviral and antibacterial protection of the body, the result of such adaptation is an increase in the risk of complications associated with some infections, including influenza [14-20]. At the same time, there is practically no information in the available literature on the assessment of the levels of these factors in ARVI, in particular, in influenza in pregnant women; their pathogenetic significance in the development of possible complications

of pregnancy, childbirth and perinatal outcomes has not been characterized. All this testifies to the high relevance of the research topic.

The aim of the study. Conduct a randomized cohort study of therapies for pregnant women with acute respiratory infections.

Materials and research methods. To achieve this goal, 45 pregnant women were examined. Pregnant women were included in the examination at 12 weeks of gestation. All patients signed written consent to participate in the experiment.

Of the total number of examined 22 pregnant women who did not have somatic pathology made up a comparative group.

23 pregnant women suffered influenza of varying severity in the I-II trimesters of pregnancy. The diagnosis of highly pathogenic influenza A H1N1 was confirmed by virologic testing. Of the 23 pregnant women, the main group consisted of 14 pregnant women who were treated with Viferon - the main group and 9 pregnant women who were treated with symptomatic therapy.

Examination of pregnant women included the collection of anamnesis, clinical, instrumental and laboratory studies, including the identification of DNA / RNA pathogens using PCR (examination of scrapings from the nasopharyngeal mucosa for Influenza virus AH1N1).

Cardiotocography and Doppler ultrasonography were performed to assess the state of blood flow in the mother-placenta-fetus system. Intranatal risk factors and complications in childbirth were characterized in terms of total duration of labor, duration of labor periods, anhydrous period, incidence of discoordination of labor, caesarean section, obstetric forceps, and fetal vacuum extraction. The level of blood loss during childbirth was assessed. The course of the postpartum period was compared in the groups of women under examination in terms of the incidence of complications. The assessment of the condition of newborns was carried out according to the Apgar scale at 1 and 5 minutes. The weight distribution of newborns was compared. The frequency of manifestations of various transient neurological disorders, intracranial changes and hypoxic ischemic encephalopathy in newborns was assessed. When studying follow-up data on the health status of children in the first year of life, we compared the indicators of the frequency of manifestations of infectious and bacterial pathology (sepsis, localized forms of infections, pneumonia). We also compared the frequency of manifestations of the main neurological syndromes in children of the first year of life. Laboratory studies included the study of the state of the hemostasis system of

the examined pregnant women with the determination of the number of platelets, activated partial thromboplastin time (APTT), the prothrombin index (PTI), concentration of fibrinogen, he soluble fibrin-monomer complex (SFMC), the level of platelet aggregation with adenosine diphosphate (ADP).

Research results. The patients included in the study were homogeneous in age, body weight and height (Table 1).

Table 1. Clinical characteristics of pregnant women with acute respiratory diseases.

indicator	Viferon (antiviral therapy)	Symptomatic therapy	p
Symptomatic therapy p			
N (%)	14 (60%)	9 (40%)	
Age, years	24,5±3,1	23,6±3,8	≤0,05
Weight, kg	78,5±12,3	76,3±10,2	≤0,05
Height, cm	165,6±14,5	162,3±13,9	≤0,05
Body mass index, kg / m ²	26,5±4,2	26,1±3,6	≤0,05

The obstetric and gynecological history included the age of onset of menstruation and sexual activity, past gynecological diseases, the number of pregnancies (their outcome), information about the present pregnancy (Table 2 and Table 3).

Table 2. Obstetric and gynecological history of patients with acute respiratory infections.

indicator	Viferon (antiviral therapy)	Symptomatic therapy	p
Age of onset of menstruation, years	14,41±1,20	14,01±1,00	≤0,05
Age of sexual debut, years	19,9±1,70	20,3±1,82	≤0,05
Real pregnancy	2,4±1,2	2,3±1,1	≤0,05

In the anamnesis, 78% of women had various gynecological and infectious-inflammatory diseases of the urogenital tract (erosion and ectopia of the cervix, chronic adnexitis, salpingo-oophoritis, etc.).

In 9 (39.4%) pregnant women, concomitant chronic diseases of the respiratory system, cardiovascular system, kidneys, gastrointestinal tract and endocrine

system were identified. In 5 (20.9%) patients, this pregnancy proceeded with complications (threat of termination, etc.) before admission to the hospital with a diagnosis of acute respiratory viral infection (ARVI). Among the etiological agents of ARVI (swab from the throat and nose for flora, polymerase chain reaction (PCR) of mucus from the pharynx and nose for viruses), adenoviruses were most often detected - 14%, parainfluenza - 12%, metapneumoviruses - 5%, coronaviruses - 4%. In 57% of cases of acute respiratory viral infections in pregnant women began acutely with an increase in body temperature to febrile values. However, in 43% of women, ARVI symptoms developed gradually over several days, which was the reason for the later admission of patients to the hospital and was often associated with the development of bacterial complications in the form of sinusitis, otitis media, acute community-acquired pneumonia or complications during pregnancy (threat of termination) ... From the analysis of the case histories, it was found that from the moment the first symptoms of acute respiratory viral infections appeared to hospitalization, it took from 2 to 7 days, on average 3.8 ± 1.2 days. In the 1st group of patients, antiviral therapy was prescribed from the first day of admission to the hospital. The effectiveness of treatment was assessed by the duration of clinical symptoms of the disease, the development of complications and pregnancy outcomes. Typical manifestations of ARVI in pregnant women upon admission to the hospital were: rhinitis - in 82% of patients, cough - in 64.2% of pregnant women, sore throat - in 57.1% of women. Dyspeptic manifestations in the form of nausea, vomiting, diarrhea occurred in 5.2% of patients. Intoxication symptoms in the form of weakness, chills, headache were recorded in 86% (20 women).

However, in patients who received Viferon® as antiviral therapy, the duration of symptoms of intoxication (fever above 38.5°C , lethargy / weakness, chills, headache) was significantly less ($p < 0.001$)

Table 3. Duration of the main clinical symptoms of acute respiratory viral infection in pregnant women of both groups.

Clinical symptom of the disease	Antiviral therapy	Symptomatic therapy	p
Fever up to 38.5°C	$3,2 \pm 0,5$	$3,5 \pm 0,58$	$\leq 0,05$
Fever above 38.5°C	$1,2 \pm 0,44$	$2,2 \pm 0,3$	$\leq 0,001$
Lethargy / weakness	$3,1 \pm 0,58$	$4,4 \pm 0,68$	$\leq 0,001$
Chills	$1,2 \pm 0,16$	$1,9 \pm 0,30$	$\leq 0,001$
Headache	$2,1 \pm 0,47$	$2,9 \pm 0,45$	$\leq 0,001$

Rhinitis	4,8±0,79	5,6±0,81	≤0,05
A sore throat	2,3±0,49	2,8±0,51	≤0,05
Pain in the eyes	1,1±0,36	1,8±0,48	≤0,05
Cough	4,2±0,74	5,6±0,92	≤0,05
Difficulty breathing, shortness of breath	1,3±0,34	2,0±0,28	≤0,05
Dyspeptic manifestations (nausea, vomiting, diarrhea)	1,1±0,45	1,7±0,23	≤0,05

As you can see, women who have had the flu were more likely to experience a number of complications. Thus, the threat of premature birth was noted in 3.8% of patients in the control group, while with influenza, the value of this indicator was significantly ($p < 0.05$) higher and amounted to 20.7% in patients with moderate severity of the disease ($p < 0.05$). With a severe degree of influenza, this complication was observed somewhat more often - in 28.1% of women.

Pregnant women in the control group did not have preterm birth, while in groups 2 and 3 their frequency was 11.6% and 19.5%, respectively. Placenta previa and its premature detachment have also been reported only in women who have had the flu. At the same time, in women with moderate disease, the frequency of these complications was 12.4 and 10.7%, respectively, in the group with severe influenza, the level of the indicator was slightly higher, amounting to 14.1 and 18.8%, respectively.

Anemia of both mild and moderate severity was also more often detected in pregnant women who had influenza compared with the corresponding indicator in the control group, while the values in the group of women with severe disease were significant ($p < 0.05$). In the control group, the frequency of polyhydramnios was only 3.8%, low water - 1.9%.

Comparison of the frequency of hospitalizations during pregnancy showed that in the control group the value of this indicator for obstetric pathology was 18.9%, in groups 2 and 3 the frequency of hospitalizations was 2 times higher - 38.9 and 40.6%, respectively ($p < 0, 05$).

Also, pregnant women with moderate and severe influenza significantly more often ($p < 0.05$) than women in the control group were hospitalized due to extragenital pathology.

Accordingly, the overall hospitalization rate in the control group was 30.2%, while in the groups of pregnant women with moderate and severe influenza it was significantly higher, amounting to 68.7 and 78.1%, respectively ($p < 0.05$).

Analysis of the results of cardiotocography showed that if the absolute majority of pregnant women in the control group (92.5%) did not reveal pathological changes, then in the group of women who had moderate influenza, the proportion of such patients was significantly ($p < 0.05$) lower - 56.4%.

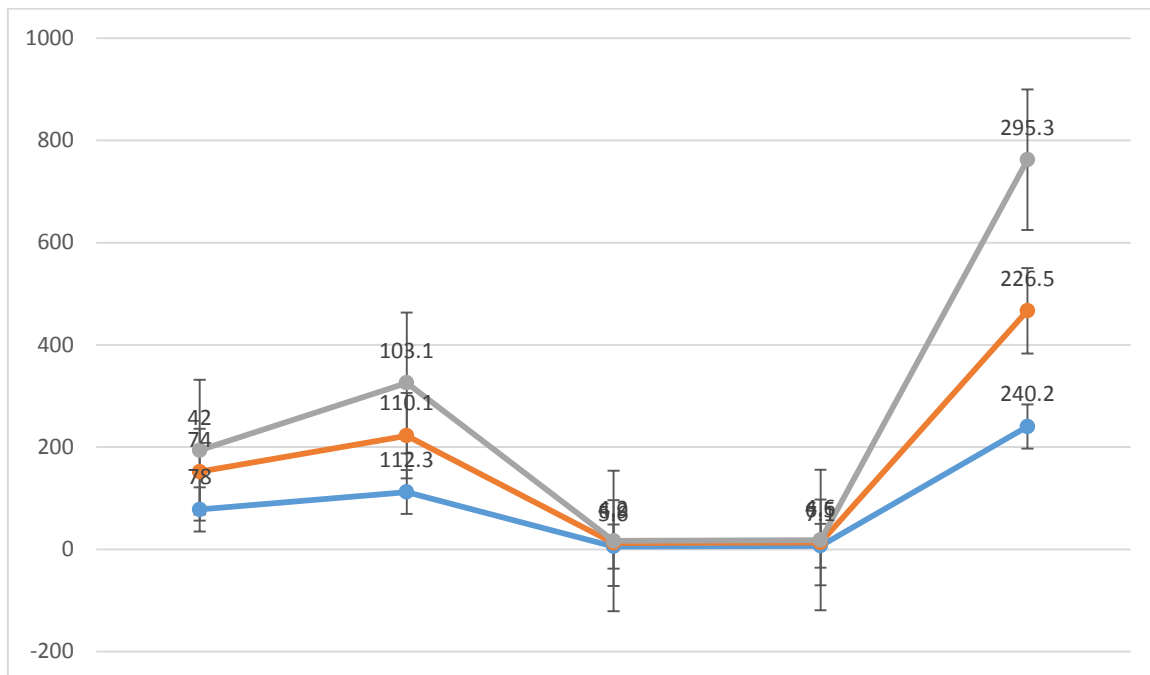
In the group of women with severe illness, the value of the indicator was even less - significantly lower ($p < 0.05$) than in the other groups.

The study of heart rate variability showed that in the control group signs of pathology were not observed, while in groups 2 and 3 the frequency of their detection was 59.1 and 62.5%, respectively. Evaluation of the frequency of manifestation of pathology by acceleration showed that in the control group deviation from the norm was observed only in 9.4% of cases. At the same time, in pregnant women who had moderate and severe influenza, the frequency of pathology detection was 51.1 and 68.7%, respectively, that is, it was significantly ($p < 0.05$) higher than in the group of healthy pregnant women.

The study of the hemostatic system in the examined women showed a number of differences in the groups of pregnant women with influenza from the corresponding values in women in the control group. The assessment of activated partial thromboplastin time (APTT) showed that the values of this parameter in groups 2 and 3 were at the level of 78 ± 7 and 74 ± 5 s, respectively, which in both cases was significantly higher than in the control - 42 ± 14 ($p < 0.05$).

In pregnant women with influenza during this period, the level of such indicators as prothrombin index (PTI), fibrinogen concentration, soluble fibrin-monomer complex (SFMC), level of platelet aggregation with adenosine diphosphate (ADP) was significantly ($p < 0.05$) higher than in the control group. At the same time, the number of platelets in pregnant women with moderate and severe influenza was 240.2 ± 1.4 and $226.5 \pm 23.4 \times 10^9 / L$, respectively. (fig. 1).

Figure: 1. State of the main links of pathogenesis in pregnant women in the third trimester of pregnancy (M ± m) (Mann-Winney criterion)



Comparison of hemostasis indicators in the 3rd trimester of pregnancy showed that the disorders identified in the 2nd trimester persisted during this period. Thus, the APTT values in the groups of patients with influenza were significantly ($p < 0.05$) higher than in the control. The PTI level in the control group was $115.5 \pm 4.9\%$ and was significantly ($p < 0.05$) higher than the corresponding indicator in the main group - $102.5 \pm 3.8\%$. The value of this indicator in pregnant women in the comparison group was $111.5 \pm 4.9\%$, and also significantly differed from the level of the main group.

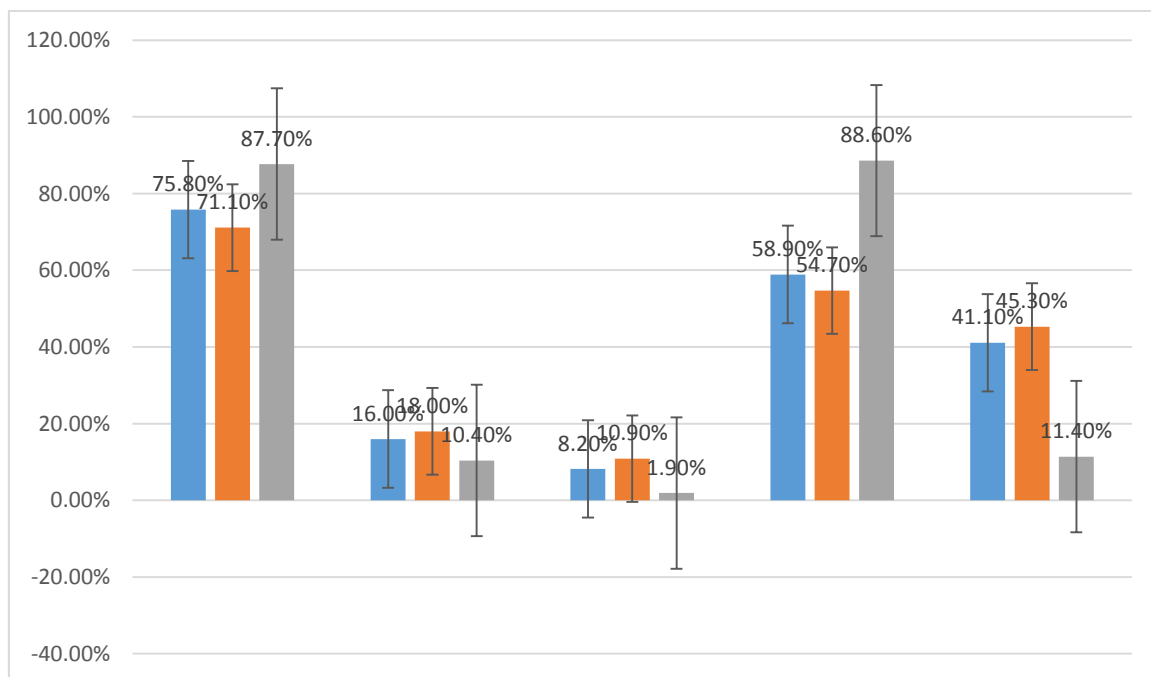
The concentration of fibrinogen was significantly higher ($p < 0.05$) than in the controls in the examined women who had had influenza of moderate severity; in pregnant women of the main group and the comparison group, there was a significant increase in the level of SFMC and a decrease in the number of platelets. The SFMC values in the group of pregnant women who had moderate and severe influenza were, respectively, 6.2 ± 0.9 and 5.7 ± 0.5 , which significantly ($p < 0.05$) exceeded the corresponding value in the control group - $4, 7 \pm 0.5$.

The number of platelets in the patients of the comparison group was reduced to $212.6 \pm 13.0 \times 10^9 / L$, which was significantly lower than the level of the main group: $267.2 \pm 20.4 \times 10^9 / L$. In women who had severe influenza, a significant ($p < 0.05$) decrease in the level of this indicator was also revealed - the number of platelets was $205.2 \pm 11.8 \times 10^7 / L$.

Evaluation of platelet aggregation showed that in the groups of pregnant women with influenza, the value of this indicator was increased relative to that in the control group, while the values of the indicator of aggregation with ristomycin in moderate and severe disease were significantly ($p < 0.05$) higher than in the control.

We also found that delivery was urgent in 87.7% of women in the control group and in a significantly smaller number of patients in the main group and in the comparison group - respectively in 75.8 and 71.1%. Preterm labor was diagnosed in 10.4% of women in the control group, in the main group - in 16.0% of the surveyed and most often in the comparison group - in 18.0% of cases. Delayed labor in the control group occurred only in 2 patients (1.9%), while in the groups of women who had influenza during pregnancy, it was significantly ($p < 0.05$) more often - in 8.2 and 10.9% surveyed (Fig. 2).

Figure: 2. Characteristics of childbirth in the examined women (Wilcoxon test)

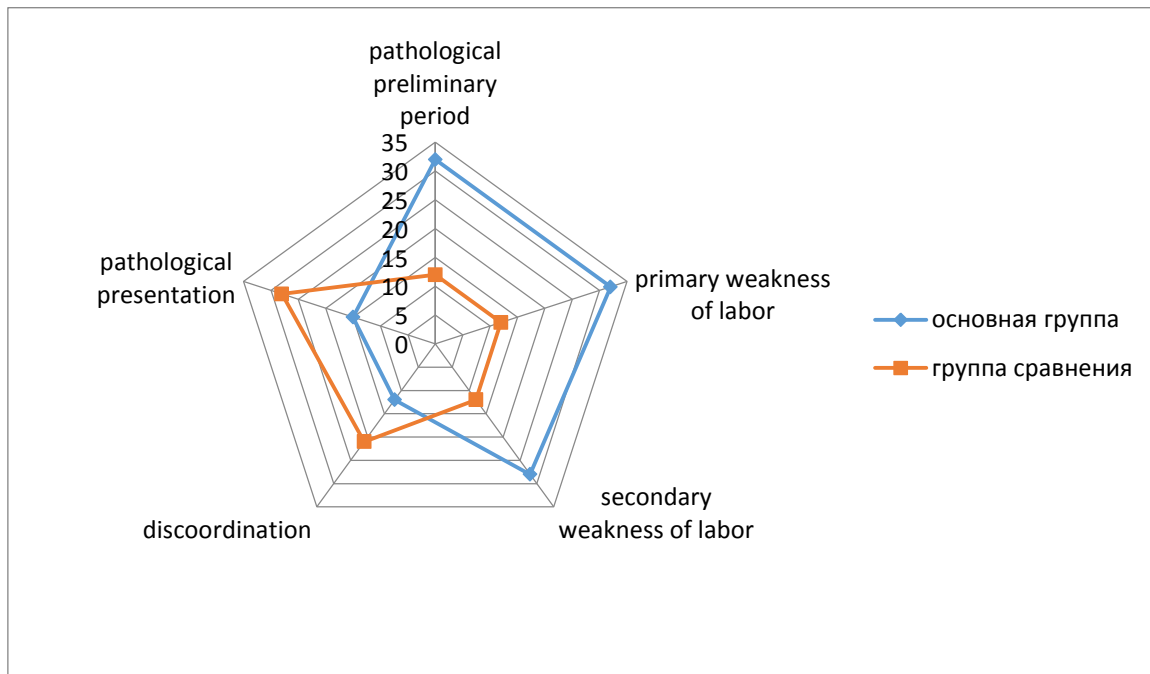


It should be noted that in terms of the total duration of labor and the periods of labor, the waterless interval, there were no significant differences between the indicators in the control group and the patients of the main and the comparison group. The analysis of complications in childbirth showed an increase in their frequency in women who had influenza. Comparison of the frequency of the observed abnormalities of labor activity showed that the majority of women in the control group (88.6%) had no abnormalities.

In the group of pregnant women who underwent influenza, childbirth proceeded reliably without anomalies ($p < 0.05$) less often - in 74.2% of

patients with an average and in 54.7% of women with a severe degree of disease (Fig. 3).

Figure: 3. Abnormalities of labor in pregnant women with influenza (Kruskal-Wallis criterion).



In the latter group, the primary weakness of labor activity was significantly ($p < 0.05$) more often than in the control group (in 15.6% of cases). In women with moderate influenza, primary weakness in labor was in 6.2% of cases, in the control group - in 3.8% of patients.

Discoordination of labor activity in the control group was not observed, while in the other groups - in 5.0% in pregnant women who had moderate influenza and in 5.5% of patients with a severe form of the disease. Cesarean section was performed in more than one third of cases in women who had severe influenza - 34.4%, which was significantly ($p < 0.05$) more often than in the control group - 17.0%.

In the group of patients with moderate influenza, the value of this indicator was 29.3%. Somewhat more often than in the control group, obstetric forceps and vacuum extraction were used in pregnant women who had had the flu in connection with the development of fetal asphyxia, although no significant intergroup differences were found. Assessment of the level of blood loss during childbirth showed that if all patients in the control group had less than 500 ml of blood loss, then in the comparison group the proportion of such women was 31.1%, in the group of those who had severe influenza, the value of this indicator was 25 %.

Conclusions: Thus, the studies carried out have shown that functional changes developing in the body of a pregnant woman with moderate and severe influenza are a background for a complicated course of pregnancy and the postpartum period. An increased incidence of pregnancy complications, changes in a number of indicators of clinical and instrumental examination of women who have had moderate and severe influenza, as well as a deterioration in the condition of newborns and the development of children in the first year of life were noted. Obviously, it is necessary to improve the tactics of managing pregnant women with influenza in order to reduce the observed negative consequences for the body of a pregnant woman and a newborn. One of the methods for in-depth study of homeostasis in this contingent may be the study of markers of endothelial dysfunction.

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