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FREQUENCY AND OUTCOMES OF EXTREMELY EARLY PRETERM BIRTH IN PREGNANT WOMEN WITH NEW CORONAVIRUS INFECTION COVID-19

DOI 10.25789/YMJ.2023.81.20

УДК 618.39-036-06:616.98:578.834.1

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The frequency of extremely early preterm birth (ERPR), their obstetric and perinatal outcomes, morphological features of the placenta in pregnant women in the city of Chelyabinsk and the Chelyabinsk region (CO) with a new coronavirus infection (NCI) in periods 1-2 and 3-4 waves of the COVID pandemic were studied. -19. The results obtained indicate that there is no increase in the frequency of ERPR in pregnant women with NCI. Delivery by caesarean section is associated mainly with the increase in acute respiratory distress syndrome (ARDS) of the mother. In the period of waves 3-4 of the COVID-19 pandemic, an increase in the perinatal mortality rate was noted compared to the period of waves 1-2 without statistical significance of these indicators. At the same time, antenatal fetal death during the 3rd-4th wave of the NCI pandemic was observed statistically significantly more often ($p=0.033$). The features of placental damage to the placentas in patients with NCI with ERPR and antenatal fetal death during the 3rd-4th wave of the pandemic are severe maternal and fetal vascular malperfusion and severe acute inflammatory lesions of the placenta (2,3 stages and 2,3 degrees).

Keywords: new coronavirus infection, extremely early preterm birth, obstetric and perinatal outcomes, placental damage.

Introduction. Presently specialists continue to actively study the effect of NCI COVID-19 on the course, outcomes of the pregnancy and fetal development. It is known that NCI of various degree of severity could be associated with the adverse obstetric and perinatal outcomes. In particular, it increases the risk of preterm birth (PB) [1, 2, 3, 8]. Extremely early PB (EEPb), that make up 5% in the structure of the general population, but are accompanied by higher rates of perinatal losses and disablement of the surviving babies, are especially unfavorable [5, 10, 12]. Data have been published on the decrease in the frequency of EEPb against the background of preventive and protective measures taken in different communities in the period of lockdown to decrease the transmission of the SARS-COV-2 virus. For the first time this was outspoken by Danish scientists based on the results of the national study (from 2.19 to 0.09 per 1,000 births, $p<0.001$) [11]. Similar data have been presented by specialists from the Netherlands, Japan, Italy, USA. In a number of other papers (California, Philadelphia, Israel, Spain and Great Britain (London), Sweden (national study) no data were obtained on the decrease in the EEPb frequency in the period of NCI COVID-19 pandemic [14]. There are more and more studies devoted to the analysis of the specifics of morphological changes in placenta

against the background of NCI, their role in adverse pregnancy outcomes [1, 7, 9, 13, 16, 17]. It should be noted that EEPb frequency in pregnant women with NCI COVID-19, obstetric and perinatal outcomes in such cases have been studied insufficiently, including the studies performed in the territory of the Chelyabinsk region (ChR).

Objective of the study: to determine the frequency of EEPb, their obstetric and perinatal outcomes in pregnant women with NCI COVID-19 in Chelyabinsk and Chelyabinsk region.

Materials and Methods. A retrospective comparative analysis of the data from the medical records (labor and delivery records, individual health records of pregnant and puerperant women, neonatal records, reports of antemortem pathology study of the biopsy (surgical) material) has been performed for 237 patients with NCI and PB, hospitalized to the maternity hospital of the Chelyabinsk Regional Clinical Hospital №2. This hospital was repurposed to a hospital providing medical assistance to pregnant, parturient, and puerperant women with NCI COVID-19, as well as to their newborn children in the territory of the Chelyabinsk city and the Chelyabinsk region. During the 1st-2nd wave of NCI pandemic (April 2020 – May 2021) 98 patients with NCI and PB underwent treatment. Within the period of the 3rd -4th wave (June 2021 – December

2021) – 139 women with NCI and PB. Frequency and outcomes of EEPB (22 weeks 0 days – 27 weeks 6 days) in the period of the 1st – 2nd and 3rd – 4th waves of COVID-19 pandemic were analyzed. The 1st study group consisted of 10 patients with NCI and EEPB in the period of the 1st – 2nd waves of pandemic. The 2nd group comprised 14 women with NCI and EEPB in the period of the 3rd – 4th waves of COVID-19 pandemic.

The inclusion criteria were: confirmed NCI COVID-19 (U07.1), gestational age – 22 weeks 0 days (22/0 weeks) – 27 weeks 6 days (27/6 weeks), check up in the maternity welfare clinic, available medical records to collect necessary information on the pregnancy course and outcomes. Exclusion criteria: possible/suspected NCI COVID-19 (U07.2/Z03.8) case. To compare the obtained results the authors used the data on the EEPB frequency and outcomes in pregnant women without NCI over the studied period from April 2020 through December 2021 inclusive, and over the 2019 year, that were provided in the annual reports of the main external obstetrician-gynecologist of the Ministry of Health of the Chelyabinsk city and ChR.

The classification proposed in 2014 by Amsterdam Placenta Workshop Group was used in the description of the placental lesions. It includes the vascular (maternal and fetal), inflammatory (inflammatory infectious and immune) and other (placental abnormalities in location, shape, umbilical cord insertion) placental lesions [15].

Statistical processing of data was performed using the statistical software package IBM SPSS Statistics-19. Standard methods of non-parametric statistics were used in the analysis of data depending on their type (Mann–Whitney U test, Fisher's exact test and Pearson chi-squared test). In checking the statistic hypotheses, the critical level of significance was assumed to be 0.05.

Results and Discussion. In general, the EEPB frequency in pregnant women with NCI (10.1% - 24/237) over the period from April 2020 through December 2021 in Chelyabinsk and ChR did not differ statistically significantly either from EEPB frequency in pregnant women without NCI over the same period of time (9.6% - 577/6,002) ($p=0.793$), or from EEPB frequency in the previous 2019 (8.2% - 280/3,433) ($p=0.287$). The median of the NCI manifestation time in group 1 and 2 was 26/5 (25/8; 27/3) weeks and 26/2 (23/9; 27/2) weeks, respectively ($p=0.278$). EEPB in pregnant women with NCI in the period of the 1st – 2nd waves

occurred in 10 cases (10.2%), during the 3rd – 4th waves – in 14 cases (10.1%) with no statistically significant differences ($p=0.974$). Information on the frequency of EEPB against the background of the manifestation of NCI COVID-19 in various regions of the Russian Federation is limited in the available literature, and their comparative analysis is difficult. In the study by A. V. Everstova et al. (2021) EEPB in pregnancy outcomes was not registered according to the results of a retrospective analysis of 82 individual records of pregnant women and puerperas with confirmed NCI (Republic of Sakha (Yakutia)) [4]. According to A. E. Esedova et al. (2022), in the republics of the North Caucasus Federal District, among pregnant women with mild and moderate NCI, EEPB was observed with a frequency of 0–1.4%. Pregnant women with severe NCI were not included in this analysis [6].

In our study, groups were comparable in medical and social characteristics. For example, median age of the pregnant with EEPB in the 1st and 2nd groups was 34.0 (33.0; 38.0) and 32.5 (27.5; 36.3), respectively ($p=0.378$). In terms of ethnicity the patients were mainly Slavs – 6 (60.0%) and 12 (85.7%) cases in the 1st and 2nd group, respectively ($p=0.056$). As for the place of residence, 6 (60.0%) and 7 (50.0%) lived in Chelyabinsk, 2 (20.0%) and 0 (0.0%) - in Magnitogorsk, 0 (0.0%) and 2 (14.3%) - in other big towns of the ChR, in small towns and settlements of the ChR - 2 (20.0%) and 5 (35.7%) of the pregnant women from the 1st and 2nd group, respectively with no statistically significant differences ($p=0.462$). The majority of them had higher (5 (50.0%) and 8 (57.1%) of women) or secondary professional (4 (40.0%) and 3 (21.4%) women) education ($p=0.661$). As for marital status, 9 (90.0%) and 13 (92.9%) ($p=0.999$) women were married in the 1st and 2nd group, respectively. As for the employment pattern, 6 (60.0%) and 8 (57.1%) women were people in work, 4 (40.0%) and 6 (42.9%) were homemakers in the 1st and 2nd group, respectively ($p=0.999$). Patients from both groups were predominantly multigravida (10 (100.0%) and 13 (92.9%), $p=0.999$), multipara (8 (80.0%) and 11 (78.6%), $p=0.999$) in the 1st and 2nd group, respectively.

Preterm birth in the past medical history was observed in 1 (10.0%) and 1 (7.1%) ($p=0.999$), artificial abortions – in 4 (40.0%) and 5 (35.7%) ($p=0.999$), spontaneous abortion – in 3 (30.0%) and 2 (14.3%) ($p=0.615$), extrauterine pregnancy – in 0 (0.0%) and 1 (7.1%) cases ($p=0.999$) in the 1st and 2nd group, respectively. Uterine scar was registered

in 4 (40.0%) and 4 (28.6%) patients in the 1st and 2nd group, respectively ($p=0.673$). In four (28.6%) cases in the 2nd group current pregnancy occurred as a result of the assisted reproductive treatment. There were no such patients in the 1st group ($p=0.114$).

There were no statistically significant differences in terms of frequency and nature of the somatic pathology: 7 (70.0%) and 11 (78.6%) cases in the 1st and 2nd group ($p=0.665$), and specifically: chronic tonsillitis was registered in 2 (20.0%) and 1 (7.1%) cases ($p=0.550$), disease of cardio-vascular system (chronic arterial hypertension) – in 3 (30.0%) and 2 (14.3%) ($p=0.615$), syndrome of the connective tissue dysplasia (mitral valve prolapse) – 1 (10.0%) and 0 (0.0%) ($p=0.417$), lower extremity varicose veins – in 1 (10.0%) and 1 (7.1%) ($p=0.999$), myopia – in 1 (10.0%) and 0 (0.0%) ($p=0.417$), thyroid disorders (asymptomatic hypothyroidism) – in 0 (0.0%) and 2 (14.3%) ($p=0.493$), urinary system pathology (non-acute chronic pyelonephritis) – in 0 (0.0%) and 2 (14.3%) ($p=0.493$), chronic iron-deficiency anaemia – in 1 (10.0%) and 2 (14.3%) ($p=0.999$), diabetes mellitus – in 0 (0.0%) and 1 (7.1%) ($p=0.999$) cases in the 1st and 2nd group, respectively.

Statistically significant differences in the body weight were revealed between the groups. Normal weight was observed in 5 (50.0%) and 2 (14.3%), excess weight – in 0 (0.0%) and 7 (50.0%), obesity – in 5 (50.0%) and 5 (35.7%) women in the 1st and 2nd group, respectively ($p=0.017$). There were no statistically significant differences in terms of Body Mass Index (BMI). Yet, there were more patients with BMI $\geq$ 25 (excess weight and obesity) during the 3rd and 4th waves of pandemic - 5 (50.0%) and 12 (85.0%) women in group 1 and 2, respectively ($p=0.085$).

Threatened miscarriage (TM) was observed in 1 (10.0%) and 2 (14.3%) ($p=0.999$), placenta praevia – in 3 (30.0%) and 0 (0.0%) ($p=0.059$), chronic placental deficiency (ChPD) – in 1 (10.0%) and 2 (14.3%) ($p=0.999$), fetal growth restriction – in 1 (10.0%) and 0 (0.0%) ($p=0.417$), amniotic fluid pathology (oligoamnios) – in 2 (20.0%) and 0 (0.0%) ($p=0.163$), cervicovaginal infections – in 4 (40.0%) and 2 (14.3%) ($p=0.192$) cases in studied group 1 and 2, respectively.

No statistically significant differences in NCI degree of severity were observed among the patients with EEPB in group 1 and 2 ($p=0.942$). Mild NCI course was registered in 2 (20.0%) and 2 (14.3%), moderate severity course – in 3 (30.0%)

and 3 (21.4%), severe course – in 3 (30.0%) and 6 (42.9%), extremely severe – in 2 (20.0%) and 2 (14.3%) cases in the 1st and 2nd group, respectively. Groups were similar in terms of pneumonia development (1st group – 8 (80.0%), 2nd group – 12 (85.7%) cases, $p=0.999$). Groups did not differ in the percentage of lung damage based on the findings of the computer tomography in dynamics either (1st group – 4 (40.0%), 2nd group – 7 (50.0%) cases, $p=0.697$).

EEPB at the 22-24/6 weeks occurred in 1 (10.0%) and 4 (28.6%), at 25-27/6 weeks – in 9 (90.0%) and 9 (71.4%) cases in the 1st and 2nd group, respectively ($p=0.358$). EEPB were spontaneous in 3 (30.0%) and 2 (14.3%) cases in the 1st and 2nd group, respectively ($p=0.615$). In terms of clinical course there were no differences between the pandemic periods. They started with premature rupture of membranes in 1 (33.3%) and 1 (50.0%), with spontaneous labor – in 2 (66.7%) and 1 (50.0%) cases in the 1st and 2nd group, respectively ($p=0.999$).

All the spontaneous EEPB ended as vaginal delivery. Medically induced vaginal EEPB occurred only in the 2nd group in 2 cases (14.3%). The induction indication was intrauterine fetal death. Medically induced EEPB via caesarean section were performed in 7 (70.0%) and in 10 (71.4%) cases in the 1st and 2nd group, respectively ($p=0.999$). Main indication for caesarean section was isolated acute respiratory distress syndrome (ARDS) of the mother: 5 (71.4%) and 9 (90.0%) cases ($p=0.360$).

The weight of the newborns in the 1st and 2nd group, respectively was 917.5 g (712.5; 990.0) and 775.0 g (611.3; 1007.5), ($p=0.229$), length – 34.0 cm (32.8; 37.0) and 33.0 cm (29.5; 35.3), ($p=0.157$), i.e. no statistically significant differences were observed.

Important parameters of the work of obstetric-gynecologic service are stillbirths and intrauterine deaths (IUD). Frequency of stillbirths was 3 (30%) and 7 (50%) cases in the 1st and 2nd group, respectively, without statistically significant differences ($p=0.421$). In all the cases (3 (100%)) in group 1 intranatal fetal death occurred; in the 2nd group – 1 (14.3%) case of intranatal fetal death and 6 (85.7%) – intrauterine fetal death ($p=0.033$). This testifies to a statistically significant predominance of intrauterine fetal death in the period of the 3rd – 4th wave of NCI pandemic.

A wide range of placental lesions was identified in all the patients in both groups in case of EEPB and NCI. They were different in the degree of manifestation

and prevalence, variety of combinations involving maternal and fetal malperfusion, maternal and fetal inflammatory response. Moderate or massive intervillous thrombosis with massive fibrin accumulation, fibrin agglutination and villous infarction, and thrombosis of the vessels of chorionic plate stand out particularly.

If there was an intrauterine fetal death, in all the cases a combination of marked maternal and fetal vascular malperfusion and severe acute inflammatory damage of the placenta (2nd, 3rd stage and 2nd, 3rd degree) occurred both for maternal and fetal inflammatory response. It resulted in decompensated placental deficiency. At the same time when there were no intrauterine deaths, the signs of the maternal and fetal stromal – vascular lesions of the placenta were manifested to a lesser degree. In half of the cases they were combined with chronic forms of placental inflammation (basal deciduitis, intervillitis).

Conclusion. Thus, no statistically significant increase in the EEPB frequency is observed in pregnant women with NCI COVID-19 of various degree of severity in the Chelyabinsk city and the Chelyabinsk region in the period of the 1st – 2nd and 3rd – 4th waves of the NCI pandemic. The level of EEPB in patients with NCI throughout the whole period under study remains stable. It does not statistically significantly exceed the EEPB level either among the population of the pregnant women without COVID-19 who were under observation from April 2020 through December 2021 ($p=0.793$), or the EEPB level registered in 2019 before the onset of the pandemic ($p=0.287$). Frequency of spontaneous EEPB in the pregnant women with NCI in the 1st and 2nd group does not differ statistically significantly and makes up 30% and 14.3% cases ($p=0.615$).

Medically induced vaginal EEPB in patients with NCI were observed only in the 2nd group in case of intrauterine fetal death. Surgery EEPB in the pregnant women with NCI were associated mainly with the increase in maternal ARDS. An insignificant increase in the intrauterine mortality rate is observed in the period of the 3rd – 4th wave of pandemic in case of EEPB relative to the period of the 1st – 2nd wave. Moreover, in the period of the 3rd – 4th wave of pandemic in case of EEPB, intrauterine fetal death occurs statistically significantly more often ($p=0.033$) in patients with NCI.

Morphological specific features of the placenta in case of the intrauterine fetal death in the period of the 3rd – 4th wave of pandemic in patients with NCI of vari-

ous degree of severity are characterized by a marked maternal and fetal vascular malperfusion and severe acute inflammatory damage to placenta (2nd, 3rd stage and 2nd, 3rd degree) in comparison to the morphological characteristics of the placenta without intrauterine losses, when in half of the cases a chronic inflammation in placenta is registered, whereas signs of the maternal and fetal stromal-vascular lesion of the placenta are manifested to a lesser degree.

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ARCTIC MEDICINE

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PROTEIN MARKERS OF NEGATIVE EFFECTS IN CHILDREN UNDER COLD EXPOSURES

DOI 10.25789/YMJ.2023.81.21

УДК 613.1: 616.1

Currently, a promising study is the identification of changes in the level of expressed proteins (omic markers) in the body under the influence of adverse factors, including climatic ones, reflecting the destabilization of homeostasis. The purpose of the study was to identify protein markers of negative effects in children living under the influence of adverse factors of the subarctic climate.

Materials and methods. A study of the proteomic profile of the blood plasma of children was carried out; statistical evaluation of the values of the relative volume of identified protein spots; establishing and evaluating a probable relationship between the change in the relative volume of identified protein spots and the impact of adverse factors of the subarctic climate.

Results and discussion. Under the influence of adverse factors of the subarctic climate in children of the observation group, relative to the indicators in children of the control group, there was a significant change in the volume of proteins (prothrombin, vitronectin, hemoglobin beta subunit, apolipoproteins A1, C-II and C-III, amyloid proteins A-1 and A- 2, P2Y purinoreceptor 12, transthyretin), the expression or decrease in production of which can cause a violation of the cascade of reactions of the blood coagulation system, a change in the development of mature forms of erythrocytes, a violation of the regulation of reverse cholesterol transport, and damage to endothelial cells.

Conclusion. The study made it possible to establish a relationship between the impact of adverse factors of the subarctic climate and the expression of proteins (apolipoprotein C-III, transthyretin, prothrombin, vitronectin, and hemoglobin β -subunit) identified in the blood plasma of children exposed to this effect. The established omic markers make it possible to predict the development of negative effects in the form of impaired homeostasis mechanisms, intracellular cholesterol esterification, insufficient oxygen supply to tissues, and endothelial dysfunction. The obtained results should be used for predicting, early detection and prevention of the development of possible diseases of the cardiovascular system, blood and hematopoietic organs associated with prolonged exposure to natural cold.

Keywords: harmful factors of subarctic climate, omic markers, predicted negative effects, children.

Introduction. In the Russian Federation approximately 40% of all regions are located in the Arctic Zone beyond

the Polar circle or are considered to have similarly harsh natural and climatic conditions. These conditions are rather severe since there are considerable temperature fluctuations, long winter, short summer, and high wind speed [6, 13]. Cold is a predominant non-specific factor which is typical for the climate on these territories. Several research works have established that exposure to cold produces certain effects on peripheral skin receptors and epithelium in the upper airways and induces specific thermoregulation reactions of the sympathetic nervous system which prevent overcooling [1, 7, 24]. When a person is exposed to natural cold, his or her body reacts to it, and this reaction involves depletion of some sections in the endogenous antioxidant protection system and excessive lipid peroxidation; also, cold receptors produce their

impulses in a different way. All this leads to systemic vascular resistance, impairs vascular permeability and regulation of vascular tone [14]. It should be noted that there are also considerable changes in hemodynamics as a component of thermal homeostasis [12]. Homeostatic systems in the body undergo complicated restructuring, and functional disorders occur in barrier organs (liver, kidneys, spleen, lungs and the immune system) [8]. As a result, there may be a growth in chronic population morbidity and cold is among basic factors causing it.

At present, there is a promising trend in tackling problems related to early detection of health disorders. This trend is identification of changes in levels of expressed proteins (omic markers) in the body under exposure to harmful factors [18, 19, 21], climatic ones included,

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