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State of immunity in pregnant women with undifferentiated connective tissue dysplasia due to cytomegalovirus infection

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Keypoints

Assessment of the state of immunity in pregnant women with undifferentiated connective tissue dysplasia and carriers of cytomegalovirus infection.

Abstract

To achieve the purpose of the study, based on developed clinical and laboratory criteria, a prospective study of the course of pregnancy and its outcomes was conducted in 62 pregnant women aged 18 to 39 years (average age 27.98±5.3) for the period from 2019 to 2022. with undifferentiated connective tissue dysplasia (UCTD), which formed a high-risk group for the development of pathology of the fetoplacental system. All pregnant women were divided into 2 groups: main (n = 36), comparison (n = 32). The first group of the study (main) consisted of 36 pregnant women with UCTD, carriers of cytomegalovirus infection, the second group (comparison) 32 pregnant women with UCTD, without carriage of cytomegalovirus infection. The control group consisted of 24 pregnant women without the presence of UCTD and cytomegalovirus infection at the time of the study. The conducted studies found that disturbances in the cellular immune system in women with UCTD increased the frequency of the infectious process. In the third trimester, women in the main group were more likely to have threatened labor (15 women (41.7±8.2% in the main group and 6 women (18.8±6.9%) in the comparison group); oligohydramnios (9 women (25 .0±7.2%) and 3 women (9.4±5.1%); intrauterine growth retardation syndrome (28 women (77.8±6.9% and 19 women (59.4±8.6 %). This was reflected in the high concentration of IgM and an increase in the relative number of CD16+ and CD20+ lymphocytes in pregnant women of the main group. Histological examination confirmed a higher frequency of infection of the ovum in pregnant women with UCTD, carriers of cytomegalovirus, which was limited to the placenta and was not accompanied by intrauterine infection of the fetus. The presence of UCTD in pregnant women with persistent infection of the herpesvirus family increases the risk of unfavorable implementation of the infectious process, and this should be taken into account when making a prognosis for the development of obstetric and perinatal complications and justifies the advisability of carrying out treatment and preventive measures during pregnancy and in the postpartum period.

Keywords

carrier, placental insufficiency, pregnancy, cytomegalovirus infection, undifferentiated connective tissue dysplasia.

Introduction

In modern obstetrics, in the structure of perinatal losses, placental insufficiency (PI) remains the main cause of perinatal morbidity in up to 40% of cases in pregnant women. According to a number of authors, the frequency of occurrence varies from 3-4% to 45% and there is a persistent upward trend [1-3]. This problem is of particular interest in pregnant women who are carriers of cytomegalovirus, due to the high prevalence of this infection among this group of women [4]. At the same time, pregnancy, as a result of the immunosuppressive effect on the body of women, tends to interfere with natural antiviral resistance and contributes to the accelerated development of viral infection [5-8]. This category of people includes pregnant women with undifferentiated forms of connective tissue dysplasia (UCTD). UCTD is a widespread pathology, reaching 25% in the general population, and women are more often affected by this disease [9]. Clinical observations have shown that patients with UCTD belong to the category of frequently ill people, which is due to disturbances in the humoral and cellular immunity system [10-12]. Based on this, determining the state of immunity and the course of the infectious process in pregnant women with UCTD and carriers of cytomegalovirus will allow optimizing the prognosis and prevention of obstetric and perinatal complications in this category of people. Of particular relevance for the early diagnosis of perinatal insufficiency is the study of the characteristics of metabolism in fluid environments and placental tissue in pregnant women with undifferentiated connective tissue dysplasia. Timely correction of identified disorders with improved tactics for managing pregnancy and childbirth will improve outcomes for the mother and fetus.

Purpose of the study: Assessment of the state of immunity in pregnant women with undifferentiated connective tissue dysplasia and carriers of cytomegalovirus infection.

Material and methods

In our work, to achieve the purpose of the study, based on developed clinical and laboratory criteria, for the period from 2019 to 2022, a prospective study of the course of pregnancy and its outcomes was conducted in 62 pregnant women aged 18 to 39 years (average age 27.98± 5.3) with UCDT, which constituted a high-risk group for the development of pathology of the fetoplacental system. Pregnant women were observed at the Department of Obstetrics and Gynecology II of the AMU. All women underwent prospective assessment of the course of pregnancy; all patients were consulted by a therapist, surgeon, and ophthalmologist to identify visceral pathology related to the clinical manifestations of UCDT. After the examination, all pregnant women were divided into 2 groups: main (n = 36), comparison (n = 32). The first group of the study (main) consisted of 36 pregnant women with UCDT, carriers of cytomegalovirus infection, the second group (comparison) 32 pregnant women with UCDT, without carriage of cytomegalovirus infection. The control group consisted of 24 pregnant women without the presence of UCDT and cytomegalovirus infection at the time of the study. The groups were formed according to the principle of continuous selection using random and typological sampling - using the method of balanced groups identical in age, nature of the course of pregnancies, parity of births, social, educational and marital status. Inclusion criteria: age from 18 to 39 years (average age 27.98±5.3 years), mild undifferentiated connective tissue dysplasia (the presence of 2 main signs of dysplasia according to the criteria of T. Milkovska-Dimitrova and A. Karkashev (1985) or from 4 to 9 points on the T.Yu. Smolnova scale (2003) [4], absence of severe pregnancy complications (severe preeclampsia), decompensated somatic pathology, informed consent of patients to participate in the study. Exclusion criteria: differentiated connective tissue dysplasia, endocrine diseases, chronic somatic pathology in the stage of decompensation, infectious diseases, infertility, multiple pregnancy, age under 18 and over 39 years, patient refusal from the

study. In the second trimester of pregnancy, venous blood was collected from the cubital vein on an empty stomach in all patients.

A second-level immunogram was performed on a Beckman Coulter Cytomics FC-500 flow cytometer with the determination of populations and subpopulations of lymphoid cells by immunofluorescence.

A qualitative study of immunoglobulins was carried out using the methods of immunoelectrophoresis and precipitation in a gel, and the quantitative content of immunoglobulins was carried out using the method of radial immunodiffusion in a gel.

The viral infection was verified on the basis of a serological study, which determined the level of specific immunoglobulins of the IgG and IgM classes for cytomegalovirus.

Carriage of cytomegalovirus was detected in 36 pregnant women. All neonates underwent clinical evaluation for cytomegalovirus infection; in doubtful cases, cytomegalovirus DNA was isolated in the biological fluids of the newborn using real-time PCR.

Results

The examined patients were aged from 18 to 39 years. The average age of pregnant women in the main group, 27.98±5.3 years, did not differ from that in the comparison group - 27.65±4.2 years and in the control group - 27.91±6.8 years (p>0.05) (Table 1).

Age	Groups					
	Main group (n=36)		Comparison group (n=32)		Control group (n=24)	
	Absolute	%	Absolute	%	Absolute	%
18-20	2	5,6±1,6	3	9,4±5,1	2	8,3±5,5
21-25	9	25,0±7,2	9	28,1±7,9	5	20,8±8,3
26-30	8	22,2±6,9	7	21,9±7,3	8	33,3±9,6
31-35	14	38,9±8,1	11	34,4±8,4	7	29,3±9,3
36-39	3	8,3±4,7	2	6,3±4,5	2	8,3±5,5

Table 1. Characteristics of pregnant women by age

The majority of the examined patients - 33 (91.7±4.5%), 30 (93.7±4.2%), 22 (91.7±3.1%) were of active reproductive age under 35 years. At the same time, almost every second pregnant woman was over 30 years of age (respectively, by group: 47.2±8.3%, 40.6±8.2%, 37.5±9.9%), which, according to the results of a number of researchers is a risk factor for the development of placental insufficiency [10, 12].

Analysis of the state of reproductive health showed that the average age at menarche in pregnant women in the groups did not differ from 13.8±1.2, 13.6±1.2, 13.6±1.1 years and did not differ from the population. In 30 (83.3±6.3%) - main, 28 (87.5±5.7%) - comparison and 20 (83.3±7.7%) patients in the control group had a menstrual cycle from the beginning of menarche was regular (p>0.05), in 12 (33.3±7.8%), in 9 (28.1±7.9%), and in 7 (29.2±9.3%), respectively established within 1.8±0.6 years, did not differ in duration before this pregnancy (28.5±2.4 days, 28.7±2.6 days, 27.8±2.2 days), as well as duration of menstrual bleeding (5.3±1.2, 5.1±1.3 and 5.0±1.2 days) (p>0.05). Menstrual bleeding in 27 (75.0±7.2%) women of the main group, in 22 (68.7±8.2%) of the comparison group and in 19 (79.2±8.2%) of the control group was moderate.

Phenotypic and visceral manifestations of UCDT in the examined women are presented in Table 2.

Stigmas of embryogenesis	Main group (n=36)		Comparison group (n=32)		Control group (n=24)	
	Abs.	%	Abs.	%	Abs.	%
Low forehead	3	8,3±4,7	3	9,4±5,1	-	-
Incised earlobes	14	38,9±8,1	8	25,0±7,6	-	-
Scoliosis	11	30,6±7,7	6	18,8±6,9	1	4,16±2,0
Mitral valve prolapse	16	44,4±8,3	11	34,4±8,4	1	4,16±2,0
Muscle wasting	8	22,2±6,9	5	15,6±6,3	-	-
Habitual dislocations	7	19,4±6,7	2	6,3±4,5	-	-
Joint hypermobility	6	16,7±6,3	4	12,5±5,9	-	-
Refractive error	9	25,0±7,2	9	28,1±7,9	2	8,3±5,5

Table 2. Phenotypic and visceral manifestations of UCDT in the examined women

The course of pregnancy in the first trimester in women of the main group was more often complicated by threatening miscarriage, requiring hospital treatment (17 women (47.22±8.3%) in the main group and 12 women (37.5±8.4%) in the comparison group, p =0.021). In the second trimester of pregnancy, women in the main group were more likely to have a threat of miscarriage (19 women (52.8±8.3%) in the main group and 9 women (28.1±7.9%) in the comparison group, p=0.031); exacerbation of herpes infection (16.7±6.3% and 3.12%, respectively, p = 0.021). In the third trimester, women in the main group were more likely to have threatened labor (15 women (41.7±8.2% in the main group and 6 women (18.8±6.9%) in the comparison group, p =0.05); oligohydramnios (9 women (25.0±7.2%) and 3 women (9.4±5.1%), respectively, p = 0.037); intrauterine growth retardation syndrome (28 women (77.8±6.9 % and 19 women (59.4±8.6%), respectively, p =0.046) Indicators of immune status in women of the compared groups are presented in Table 3.

Immunological indicators	Main group (n=36)	Comparison group (n=32)	Control group (n=24)
Leukocytes	5,46±1,1*	6,34±1,2	6,93±1,3
Lymphocytes	1,8± 0,8*	2,3±0,7	2,4±0,8
Lymphocytes, %	28,4±7,3	32,6±8,2	34,2±7,2
CD3, абс	0,8±0,3*	1,2±0,3 *	1,5±0,4
CD3, %	42,8±8,2*	48,2±8,6*	62,2±12,4
CD4, абс	0,7±0,2*	0,8±0,4	0,9±0,4
CD4, %	31,8±4,3*	35,4±3,3	38,4±4,2
CD4/CD8	1,48±0,3*	1,74±0,3	1,86±0,4
CD8, абс	0,32±0,1*	0,48±0,3	0,67±0,4
CD8, %	19,6±2,4	20,8±2,4	22,4±3,4
IgM, г/л	1,88±0,24*	1,70±0,16	1,48±0,16
IgA, г/л	1,18±0,22*	1,32±0,24*	1,86±0,26
IgG, г/л	9,12±1,2	8,6±1,14	11,2±0,42

Table 3. Indicators of humoral and cellular immunity in the examined women (M±σ). Note. * – p < 0.001

Childbirth outcomes for the fetus and anthropometric indicators of newborns in the examined women are presented in Table 4.

Parameters	Main group (n=36)	Comparison group (n=32)	Control group (n=24)	P1	P2
Anthropometric data of newborns					
Average weight, g	3002,4±564	3354,6±526	3332,2±463	0,000	0,006
Average height, cm	50,2±3,2	52,8±2,8	51,9±1,9	0,000	0,054
Head circumference, cm	31,6±1,9	34,6±1,4	33,5±1,4	0,000	0,000
Chest circumference	32,2±1,8	32,8±1,6	33,2±1,4	0,000	0,022
Apgar score in the first minute					
Up to 7 points	19,4%	6,3%	-	0,022	0,032
7 points and above	80,6%	93,7%	100%	0,022	0,032
Apgar score at five minutes					
Up to 7 points	16,7%	-	-	0,021	0,072
7 points and above	83,3%	100%	100%	0,021	0,072

Table 4. Condition of newborns in the examined women (M±σ). Note. P1 – main group and comparison group; P2 – main and control group

Data from the results of enzyme immunoassay for placental cytomegalovirus in the examined women are presented in Table 5.

Parameters	Main group (n=36)	Comparison group (n=32)	Control group (n=24)
Immunofluorescence reaction to CMV of the placenta			
Positive	44,4%	-	-
Negative	55,6%	100	100
Enzyme immunoassay of placental blood for CMV			
CMV	19,4	-	-

Table 5. Results of enzyme immunoassay for placental cytomegalovirus in examined women

When examining newborns in all groups, not a single case of intrauterine infection of the fetus was registered.

Discussion

Connective tissue dysplasia is a genetically determined systemic process, which is a common disease, the clinical manifestations of which occur in 26-80% of the general human population [3-6]. This spread in frequency has its own explanation. Modern classification identifies two main forms of CTD: differentiated and undifferentiated. Differentiated forms of CTD are represented by Marfan syndrome, Ehlers–Danlos syndrome, osteogenesis imperfecta, flaccid skin, and more than 100 more syndromes in the description of hereditary human diseases by McCusick [4]. Diagnosis of this group of diseases is usually not difficult, since they are associated with damage to a specific type of collagen, have clear clinical manifestations and well-studied genetic markers. The opposite of them are undifferentiated forms of connective tissue dysplasia (UCTD). The difference between UCTD is the multiplicity and polysystemic nature of their clinical manifestations, and the damage to different loci of genes encoding collagen synthesis, which complicates their genetic classification and diagnosis [2]. This was reflected in the results of the study, which showed the predominance of valvular, thoracodiaphragmatic, muscular, cosmetic syndromes and pathology of the visual organs in women with UCTD. Interest in the course of the

infectious process in pregnant women with UCTD, carriers of CMV, is due to the difference in treatment and diagnostic approaches that are used for the persistence of viral infection in such patients. There is an opinion that there is no relationship between the clinical manifestations of a viral infection in the mother and the risk of intrauterine damage to the fetus, and antibodies to the infectious agent detected in the mother protect the fetus. It is believed that the functional state of the immune system in UCTD is often characterized by its insufficiency, although the mechanisms that explain it remain undiscovered to this day [9-11]. The detected decrease in the number of CD3+ lymphocytes in patients of the main group and the comparison group shows that this feature in women with UCTD persists during pregnancy. When comparing immunity indicators in pregnant women of three groups, it was revealed that in patients with UCTD, carriers of CMV, there was the greatest decrease in the absolute number of leukocytes and lymphocytes; deficiency of T-lymphocytes (CD3), CD4+ and CD8+ cells, decreased CD4+/CD8+ ratio, low IgA content. These results can be explained both by the primary immunodeficiency of these patients and by the influence of CMV on immune cells. It is known that the “merit” of CMV is the suppression of the synthesis of various cellular proteins, blocking the action of interferon, disruption of the function of immunocytes when they are directly infected, which may be accompanied by aggravation of systemic or local immunodeficiency [5-7]. In turn, these disturbances in the cellular immune system in women with UCTD increased the frequency of the infectious process. This was indirectly manifested by a complicated pregnancy, an increased frequency of clinical manifestations of fetoplacental insufficiency, and worse perinatal outcomes; was accompanied by more frequent exacerbations of viral infection during pregnancy, which was reflected in a high concentration of IgM and an increase in the relative number of CD16+ and CD20+ lymphocytes in pregnant women of the main group. Histological examination confirmed a higher frequency of infection of the fetal egg in pregnant women with NFDST, carriers of CMV, which was limited to the placenta and was not accompanied by intrauterine infection of the fetus. Thus, the presence of UCTD in pregnant women with persistent infection of the herpesvirus family increases the risk of unfavorable implementation of the infectious process, therefore it should be taken into account when making a prognosis for the development of obstetric and perinatal complications and justifies the feasibility of carrying out treatment and preventive measures during pregnancy and in the postpartum period.

References

1. Antunes, M. Undifferentiated connective tissue disease: state of the art on clinical practice guidelines. / M.Antunes , C.A.Scirè, R.Talarico [et al.] // RMD Open. 2019; 4 (Suppl 1), p.786.
2. Ben Mbarek Makrem, Pahnova L.R. Diagnostic value of neopterin in atopic dermatitis in children. // The international scientific conference for students and young researchers in English «Topical issues of medicine». Stavropol, 2017.- P-6
3. Kudinova, EG, Karbyshev, IA, Sorokina, EA. The course of early pregnancy in women with undifferentiated forms of connective tissue dysplasia .// Mezhdunarodnyi zhurnal eksperimental’nogo obrazovaniya. 2010;5:17-19. (In Russ.)].
4. Kerimkulova, N.V., Nikiforova, N.V. The course of pregnancy and delivery in women with undifferentiated connective tissue dysplasia. // Vestnik Ivanovskoi meditsinskoi akademii. 2011; 6: 40-41. (In Russ.)].
5. Demura, T.A., Kogan, E.A., Donnikov, A.E. Clinicomorphological and molecular genetic characteristics of the myometrium in insolvency uterine scar after cesarean section in women with signs of undifferentiated forms of connective tissue dysplasia. // Arkhiv patologii. 2012;3:18-21. (In Russ.)]
6. Naumova, L.A., Osipova, O.N., Klinnikova, M.G. Immunistochemical Analysis of the Expression of

TGFβ, Galectin-1, Vimentin, and Thrombospondin in Gastric Cancer Associated with Systemic Undifferentiated Connective issue Dysplasia. // Bull Exp Biol Med. 2019 Apr 26. p. 1007

7. Demura, T.A. The morphological substrate and molecular mechanisms of impaired pregnancy outcomes in women with hereditary thrombophilias and undifferentiated connective tissue dysplasia. / T.A.Demura, E.A.Kogan, A.S.Zanozin [et al], Arkh Patol. 2018;80(5):33-36.
8. Pepmueller, P.H. Undifferentiated connective tissue disease, mixed connective tissue disease, and overlap syndromes in rheumatology. // Mo Med. 2016;113(2):136–140
9. Radin, M. A multicentre study of 244 pregnancies in undifferentiated connective tissue disease: maternal/fetal outcomes and disease evolution. / M.Radin, K. Schreiber, I.Cecchi [et al] // Rheumatology. 2020; p.1–7.
10. Sciascia, S. The impact of hydroxychloroquine treatment on pregnancy outcome in women with antiphospholipid antibodies. / S.Sciascia, D.J.Hunt, E.Talavera-Garcia [et al] //Am J Obstet Gynecol. 2016; 214(2):271–273.
11. Solyeyko, O.V. Assessment of rehabilitation potential in patients with vascular dysfunction caused byun differentiated connective tissue dysplasia. / O.V.Solyeyko, I.P.Osypenko, T.V.Galych [et al] // Wiad Lek. 2017;70(2 pt 2):282-285.
12. Wong, L.F. The effect of a very short interpregnancy interval and pregnancy outcomes following a previous pregnancy loss. / I.F.Wong, K.C.Schliep, R.M.Silver [et al] // Am J Obstet Gynecol. 2015;212(3):371–375.