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EXTRAGENITAL AND INFECTIOUS FACTORS MAY PROVOKE MISCARRIAGE

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Adverse reproductive outcome before term is a polyetiological pathology associated with demographic crisis. Some adverse outcomes include perinatal and neonatal infant mortality, major morbidity and mortality of children under two years, violation of psychomotor and physical development, cognitive disturbances and disability of children under age five. Finding ways to solve these issues remain a priority. The research involved two female groups. The experimental group included 403 women after the involuntary termination of pregnancy, premature birth or in case of threat of miscarriage; the control group included 402 women with physiological course of pregnancy and parturient with full-term pregnancy. The study required the application of systemic approaches and methods including structural, logical, medical and statistical analyses. The survey revealed more than 20 infectious risk factors and more than 70 factors of extragenital origin. The most significant infectious pathologies included COVID-19 (36.23 ± 2.29% and 14.93 ± 1.78%), herpes type 1 (5.96 ± 1.18% and 1.0 ± 0.50%), toxoplasmosis (4.22 ± 1.0% and 1.0 ± 0.50%) and chlamydial infection (4.22 ± 1.0% 0.50 ± 0.35%) in the experimental and control groups, respectively (P < 0.01). The most significant extragenital pathologies involved autoimmune thyroiditis (8.68 ± 1.40% and 0.75 ± 0.43%), type 1 diabetes mellitus (2.23 ± 0.74% and 0%) and allergic rhinitis/sinusitis (3.97 ± 0.97% and 0.50 ± 0.35%) in the experimental and control groups, respectively (P < 0.01). Obtained results will be used in the development of a personified risk-oriented model for the prevention of preterm pregnancy loss.

K e y w o r d s: adverse reproductive outcomes before term, risk factors, extragenital pathology, infectious pathology, risk-oriented model.

Adverse reproductive outcome before term (miscarriage and premature birth) is a polyetiological pathology that leads to demographic crisis as well as perinatal and neonatal mortality of babies [1], severe morbidity and mortality of toddlers under the age of two, impaired psychomotor and physical development, cognitive impairment and disability of children under the age of five [2]. Every year, approximately 15 million premature babies are born worldwide [3], and 23 million miscarriages occur globally every year, translating to 44 pregnancy losses each minute [4]. The costs of miscarriage affect individuals, health-care systems and society. The frequency of miscarriage remains at a high level in most countries of the world and risk of self-reported pregnancy loss has increased in the U.S. [5]. According to the analysis of the dynamics of adverse reproductive outcomes before term rates in Ukraine, there is an increase in the index of the ratio of cases of adverse reproductive outcomes be-

fore term to the total number of pregnancies (cases of reproductive outcomes per 100 pregnancies) from 5.50 in 2014 to 6.22 in 2021 [6], which defines this pathology as a priority in search of ways to solve it both in Ukraine and in many countries of the world [7].

Materials and Methods

In the course of the study, two groups of women were formed. The respondents in this study were mainly women who are residents of the Lviv region (including the city of Lviv) and received obstetric and gynecological care in health care institutions of Lviv and the Lviv region. The main group consisted of 403 women after spontaneous abortion, premature birth or threat of miscarriage, while the control group included 402 women with a physiological course of pregnancy and parturient with a full-term pregnancy.

A proper questionnaire was developed for the research in compliance with the ethical principles of the Declaration of Helsinki. The questionnaire was given a positive approval by the Commission on Ethics of Scientific Research, Experimental Development and Scientific Works at the Danylo Halytsky Lviv National Medical University (Protocol No. 1 from January 25, 2021). Pilot testing of the questionnaire in health care institutions of Lviv was performed in order to confirm its reliability and validity prior to the implementation of the main part of the study.

With respect to anonymity, all respondents signed consent to conduct the study and filled out identical questionnaires, which allowed us to analyze extragenital and infectious risk factors that could have an adverse effect on the course of pregnancy. The sociological method, methods of systemic approach and structural, logical, medical and statistical analysis were used in the study.

The results of the questionnaire responses are presented in the form of percentages and a 95% confidence interval, which was calculated using the Wald or Fisher's exact tests. The difference between groups of categorical indicators was studied using a frequency table, and reliability was established using Pearson's chi-squared test. If the expected value in one of the cells of the frequency table was less than five, Fisher's exact test was used.

The confidence level was set at 95%. The difference between the samples was considered significant at $P < 0.05$. All statistical calculations and the formation of individual graphs were carried out using the RStudio v. 1.4.1106 software. Excel 2010 spreadsheets were used to design tables and most figures.

Results

During the survey, information was collected on more than 20 infectious risk factors and more than 70 factors of extragenital origin. Infectious pathology was anamnestic in nature. None of the respondents noted the presence of an acute infectious pathology or a recurrence of a chronic infection during pregnancy, i.e., the first, second or third trimesters. Regarding diseases caused by TORCH infections, a reliably significant difference in incidence rates between experimental and control groups was found for toxoplasmosis amounting to 4.22% (2.48–6.40) in the experimental group and 1.0% (0.26–2.20) in the control group ($P < 0.01$). Herpes type 1 was noted by 5.96% (3.86–8.47) women of the experimental group and by 1.0% (0.26–2.20) of respondents of the control group ($P < 0.01$). We did not find a significant difference between the incidence of herpes type 2 in the experimental group 0.99% (0.26–2.19) and the control group 0.5% (0.05–1.42) ($P > 0.05$).

There was a significant difference between the incidence of chlamydial infection amounting to 4.22% (2.48–6.40) and 0.5% (0.05–1.42) ($P < 0.01$) in experimental and control group, respectively, and trichomoniasis 0.99% (0.26-2.19) and 0% (0–0.24) ($P < 0.05$) in experimental and control groups, respectively, with the most significant results presented in Fig. 1. The incidence of the following infections did not show a reliable difference between indicators and was not significant ($P > 0.05$): cytomegalovirus 1.99% (0.85–3.57) in the experimental group and 1.0% (0.26–2.20) in the control group, rubella 2.98% (1.54–4.86) in the experimental group and 1.74% (0.70–3.25) in the control group, candidiasis 11.66% (8.72–14.97) and 8.71% (6.15–11.66) in the experimental and control groups, respectively.

The analysis of the indicators of other infectious diseases made it possible to single out a reliably significant difference and therefore the negative impact (Fig. 2) of such an infectious disease as COVID-19, in which the indicators amounted to 36.23% (31.61–40.98) in the experimental group and 14.93% (11.61–18.57) in the control group ($P < 0.01$). The difference between the incidence of influenza in the experimental group (17.62% (14.06–21.49)) and the

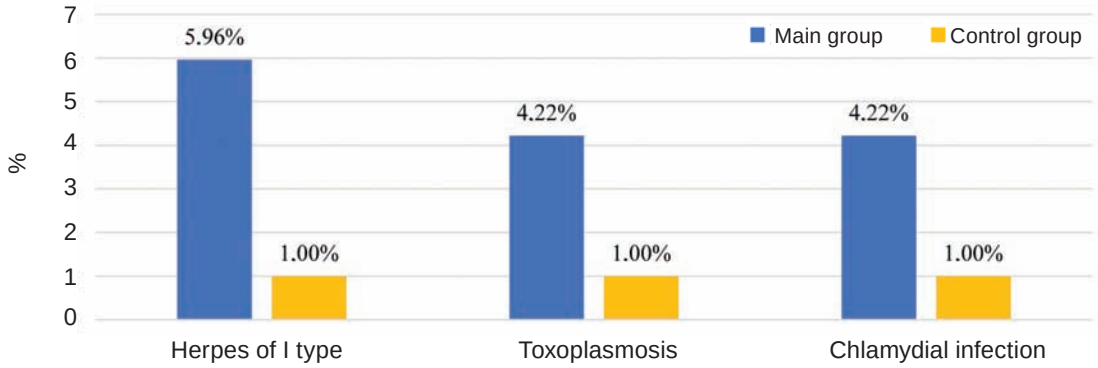

Fig. 1. TORCH and sexually transmitted infections that provoke the adverse reproductive outcomes before term (P < 0.01)

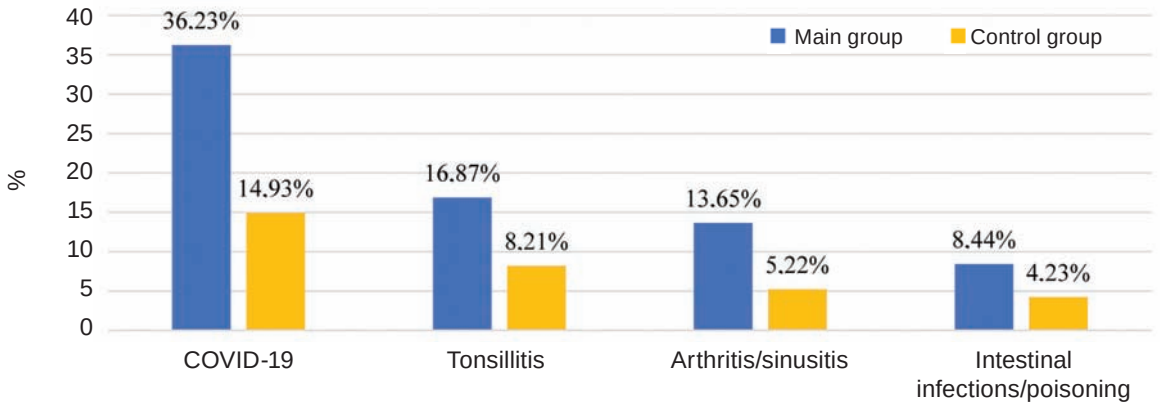

Fig. 2. COVID-19 and diseases of infectious origin that provoke the adverse reproductive outcomes before term (P < 0.01)

control group (10.70% (7.87–13.90)) was significant ($P < 0.01$). A probable difference ($P < 0.01$) between the experimental and control groups was also proven regarding other diseases of infectious origin, such as: tonsillitis 16.87% (13.38–20.68) in the experimental group and 8.21% (5.73–11.09) in the control group, sinusitis/acute sinusitis 13.65% (10.47–17.17) in the experimental group and 5.22% (3.27–7.61) in the control group and intestinal infections/poisoning 8.44% (5.93–11.34) and 4.23% (2.48–6.41) in the experimental and control groups, respectively. The findings are presented in Table 1.

Investigating risk factors that could be provoked by extragenital pathology, we collected information about diseases systematically including cardiovascular pathology, diseases of the respiratory and digestive systems, endocrine pathology, diseases of the urinary system, dysfunctions and diseases of immune genesis, neurological disorders, etc. The results are presented in Table 2.

Among the large number of pathologies studied, the most significant was autoimmune thyroiditis, the presence of which was noted by 8.68% (6.14–11.63) of women in the experimental group and 0.75% (0.14–1.82) in the control group ($P < 0.01$). Type 1 diabetes was noted in 2.23% (1.02–3.90) of the women of the experimental group and type 2 diabetes in 0.99% (0.26–2.19) of the respondents of the same group, while no women of the control group reported the presence of any type of diabetes at 0% (0–0.24) ($P < 0.01$), which is shown in Fig. 3.

Data in Fig. 4 indicate the impact of allergic rhinitis/sinusitis, which was noted in 3.97% (2.29–6.09) and 0.50% (0.05–1.42) of women of the experimental and control groups, respectively ($P < 0.01$). The presence of ABO/Rhesus conflict was reported by 2.23% (1.02–3.90) of respondents of the experimental group, while no one in the control group noted the presence of this pathology at 0% (0–0.24) ($P < 0.01$).

Table 1. TORCH and sexually transmitted infections and diseases of infectious origin that may provoke the adverse reproductive outcomes before term

№	Pathology	Main group		Control group		Probability, *P*
		Prevalence of pathology (%)	Confidence interval	Prevalence of pathology (%)	Confidence interval	
1	Influenza	17.62	14.06–21.49	10.70	7.87–13.9	$P < 0.01$
2	Trichomoniasis	0.99	0.26–2.19	0.00	0–0.24	$P < 0.05$
3	Rubella	2.98	1.54–4.86	1.74	0.70–3.25	$P > 0.05$
4	Cytomegalovirus	1.99	0.85–3.57	1.00	0.26–2.2	$P > 0.05$
5	Herpes of II type	0.99	0.26–2.19	0.50	0.05–1.42	$P > 0.05$
6	Candidiasis	11.66	8.72–14.97	8.71	6.15–11.66	$P > 0.05$

Table 2. Extragenital pathologies, endocrine and immune disorders that may provoke the adverse reproductive outcomes before term

№	Pathology	Main group		Control group		Probability, *P*
		Prevalence of pathology (%)	Confidence interval	Prevalence of pathology (%)	Confidence interval	
1	Colitis	0.99	0.26–2.19	0.00	0–0.24	$P < 0.05$
2	Hypotension	0.99	0.26–2.19	0.00	0–0.24	$P < 0.05$
3	Bilateral nephroptosis	0.99	0.26–2.19	0.00	0–0.24	$P < 0.05$
4	Nodular goiter	3.23	1.73–5.17	2.99	1.55–4.87	$P > 0.05$
5	Pyelonephritis	8.19	5.71–11.06	10.45	7.65–13.62	$P > 0.05$
6	Gastritis	12.66	9.59–16.07	13.43	10.28–16.94	$P > 0.05$

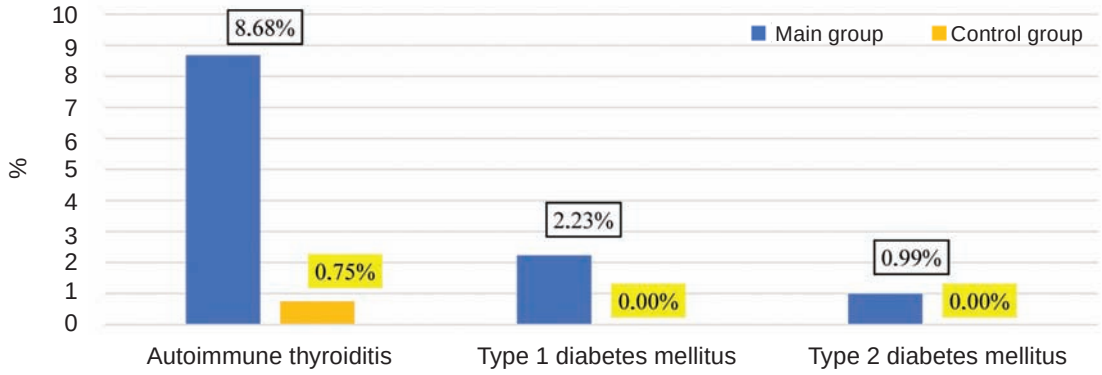

Fig. 3. The most significant extragenital pathologies that provoke the adverse reproductive outcomes before term ($P < 0.01$)

Likewise, four respondents in the experimental group remarked the presence of bronchial asthma, systemic lupus erythematosus, colitis, hypotension or bilateral nephroptosis, which amounted to 0.99% (0.26–2.19) each, while no cases with the above-listed pathologies were registered in the control group at 0% (0–0.24) ($P < 0.01$).

Respondents of both groups noted a history of pyelonephritis in 8.19% (5.71–11.06) and 10.45% (7.65–13.62) of women in the experimental and control groups, respectively, but the difference between the groups was not significant ($P > 0.05$). The influence of gastritis on the course of pregnancy remained unproven. The presence of this pathology

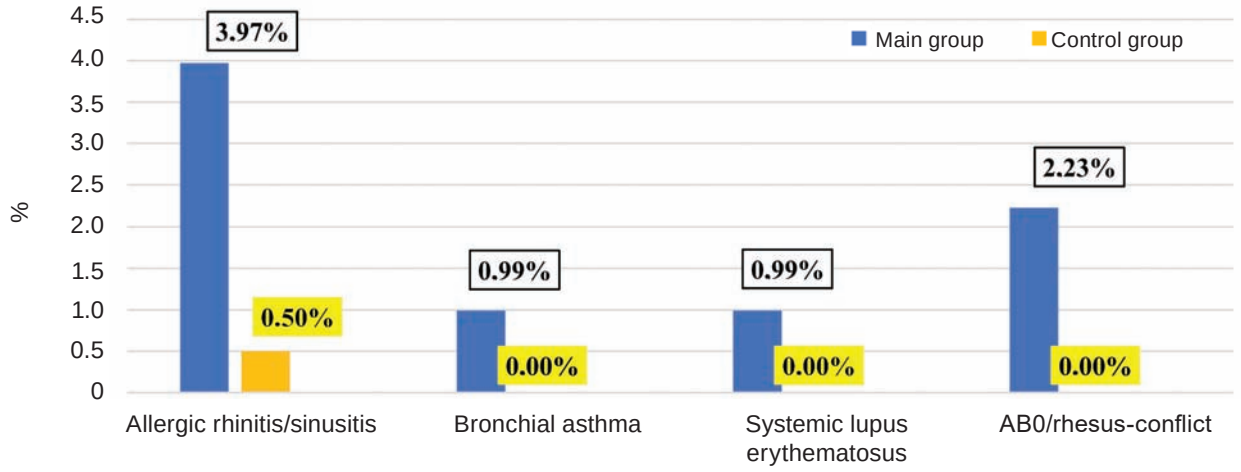

Fig. 4. Immune disorders and allergic diseases that may provoke the adverse reproductive outcomes before term ($P < 0.05$)

was noted by 12.66% (9.59–16.07) of the experimental group and 13.43% (10.28–16.94) of the control group ($P > 0.05$). The result was similar for nodular goiter, which was noted in 3.23% (1.73–5.17) and in 2.99% (1.55–4.87) of women of the experimental and control groups, respectively, with a nonsignificant difference ($P > 0.05$).

Discussion

We compared our results with the data of international studies. According to the findings of a retrospective cohort study by Tang J. in China [8], which was conducted before conception among 634,030 women who had already given birth to one child and did not have chronic diseases (diabetes, hypertension, etc.), participants were divided into groups according to their body mass index and fasting glucose level before pregnancy. Compared to mothers with normal weight and normoglycemia, mothers with underweight and elevated glucose levels had a 14.0% higher risk of preterm birth (1.14 (1.02–1.27)), while mothers with obesity and elevated glucose levels had a 45.0% higher risk of preterm birth (1.45 (1.18–1.78)). Insufficient weight, regardless of glucose and obesity with elevated fasting glucose, was associated with an increased risk of preterm birth, but the association differed by maternal age. Our research differs in the fact that women were included in the research groups regardless of obstetric, gynecological and somatic anamnesis, and we proved the negative effect of elevated glucose levels on the course of pregnancy.

The data provided by Schjenken J. E. [9] are interesting as they indicate the contribution of endocrine disorders to adverse pregnancy outcomes, as well as infertility and reduced fertility. In this study, Schjenken J. E. et al. put special attention precisely on the key elements of the immune response associated with pregnancy and immune dysregulation among the effects that can be provoked by endocrine disorders because of the critical importance of the mother's immune response during pregnancy. Research to identify the importance of the immune effects of endocrine disorders in reproduction and pregnancy is consistent with the World Health Organization's recommendation to improve knowledge about endocrine disorders and human health.

Our research also made it possible to isolate and prove the significant impact of endocrine and immune disorders (autoimmune thyroiditis, ABO/Rhesus conflict, allergic rhinitis, etc.) on the adverse course of pregnancy.

A review by Tang W. et al. [10] was registered and complied with the Cochrane guidelines. They searched three databases to quantify adverse outcomes associated with chlamydial infection. And, as a result, chlamydial infection was positively associated with almost all of the 12 adverse pregnancy and fertility outcomes covered including stillbirth and spontaneous abortion, the researchers also noted that the risk of chlamydia-related adverse outcomes is higher in low- and middle-income countries compared to high-income countries.

According to the results of a prospective cohort study conducted by Jaiswal N. [11], pregnant women

with an uncomplicated pregnancy, but with a positive SARS-CoV-2 result with an asymptomatic or moderately symptomatic course of the disease, had signs of placental damage at the microscopic level. This damage to the placenta, in the opinion of non-indoctrinators, did not lead to poor pregnancy outcomes.

Meanwhile, studies by Bouachba A. [12] noted poor pregnancy outcomes, namely cases of intrauterine death and extremely premature newborns, and fetal growth retardation without clinical and biological signs of SARS-CoV-2 infection. Scientists have linked SARS-CoV-2 to a rare set of placental lesions that can lead to fetal death, premature birth or growth restriction. Our study included not only SARS-CoV-2 exposure during pregnancy, but also a history of COVID-19, which did not reduce its negative impact on the course of pregnancy.

Conclusions. According to the results of the study, the most significant pathologies determined for infectious risk factors were COVID-19, herpes type 1, toxoplasmosis and chlamydial infection. The most significant extragenital risk factors revealed in the study include autoimmune thyroiditis, diabetes and allergic rhinitis/sinusitis. These findings will be used when forming groups with an increased risk of adverse reproductive outcomes before term among women of reproductive age and in the development of a personalized risk-oriented model of prevention of adverse reproductive outcomes before term.

Conflict of interest. Authors have completed the Unified Conflicts of Interest form at http://ukr-biochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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ЕКСТРАГЕНІТАЛЬНІ ТА ІНФЕКЦІЙНІ ФАКТОРИ, ЩО МОЖУТЬ СПРОВОКУВАТИ НЕВИНОШУВАННЯ ВАГІТНОСТІ

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Невиношування вагітності є поліетіологічною патологією, яка пов'язана з демографічною кризою. Невиношування вагітності являється однією з причин перинатальної та неонатальної смертності немовлят, зростання захворюваності і смертності дітей до двох років, порушення психомоторного та фізичного розвитку, когнітивних розладів та інвалідності дітей віком до п'яти років. Пошук шляхів вирішення цих проблем залишається пріоритетним. Досліджували дві жіночі групи. До дослідної групи увійшли 403 жінки після мимовільного переривання вагітності, передчасних пологів або при загрозі викидня, а до контрольної групи – 402 жінки з фізіологічним перебігом вагітності та доношеною вагітністю. У дослідженні застовано методи системного підходу, структурно-логічного, медичного та статистичного аналізів. Під час обстеження виявлено понад 20 інфекційних факторів ризику та понад 70 факторів екстрагенітального походження. Найбільш значимими інфекційними патологіями були COVID-19 (36,23 ± 2,29% та 14,93 ± 1,78%), герпес 1 типу (5,96 ± 1,18% та 1,0 ± 0,5%), токсоплазмоз (4,22 ± 1,0% та 1,0 ± 0,50%) та хламідійна інфекція (4,22 ± 1,0% та 0,50 ± 0,35%) в дослідній та контрольній групах відповідно ($P < 0,01$). Найбільш значимими екстрагенітальними патологіями були аутоімунний тиреоїдит (8,68 ± 1,40% і 0,75 ± 0,43%), цукровий діабет 1 типу (2,23 ± 0,74% і 0%) та алергічний риніт/синусит (3,97 ± 0,97% і 0,50 ± 0,35%) у дослідній та контрольній групах відповідно ($P < 0,01$). Отримані результати будуть використані при розробці персоніфікованої ризик-орієнтованої моделі попередження невиношування вагітності.

Ключові слова: невиношування вагітності, фактори ризику, екстрагенітальна патологія, інфекційна патологія, ризик-орієнтована модель.

References

1. Tietzmann MR, Teichmann PDV, Vilanova CS, Goldani MZ, Silva CHD. Risk Factors for Neonatal Mortality in Preterm Newborns in The Extreme South of Brazil. *Sci Rep.* 2020; 10(1): 7252.
2. Torchin H, Ancel PY, Jarreau PH, Goffinet F. Epidemiology of preterm birth: Prevalence, recent trends, short- and long-term outcomes. *J Gynecol Obstet Biol Reprod (Paris).* 2015; 44(8): 723-731. (In French).
3. Torchin H, Ancel PY. Epidemiology and risk factors of preterm birth. *J Gynecol Obstet Biol Reprod (Paris).* 2016; 45(10): 1213-1230. (In French).
4. Quenby S, Gallos ID, Dhillon-Smith RK, Podesek M, Stephenson MD, Fisher J, Brosens JJ, Brewin J, Ramhorst R, Lucas ES, McCoy RC, Anderson R, Daher S, Regan L, Al-Memar M, Bourne T, MacIntyre DA, Rai R, Christiansen OB, Sugiura-Ogasawara M, Odendaal J, Devall AJ, Bennett PR, Petrou S, Coomarasamy A. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. *Lancet*. 2021; 397(10285): 1658-1667.
5. Rossen LM, Ahrens KA, Branum AM. Trends in Risk of Pregnancy Loss Among US Women, 1990-2011. *Paediatr Perinat Epidemiol*. 2018; 32(1): 19-29.
6. Timchenko NF, Gutor TG. Dynamics of miscarriage among the female population of fertile age in Ukraine and in Lviv region in 2014–2021. *Acta Medica Leopoliensia*. 2022; 28(3-4): 72-86.
7. Lorthe E, Torchin H, Delorme P, Ancel PY, Marchand-Martin L, Foix-L'Hélias L, Benhammou V, Gire C, d'Ercole C, Winer N, Sentilhes L, Subtil D, Goffinet F, Kayem G. Preterm premature rupture of membranes at 22-25 weeks' gestation: perinatal and 2-year outcomes within a national population-based study (EPIPAGE-2). *Am J Obstet Gynecol*. 2018; 219(3): 298.e1-298.e14.
8. Tang J, Chen R, Yu Y, Bao W, Tiemeier H, Rodney A, Zhu X, Li M, Huang D, Zhao Q. Associations of pre-pregnancy impaired fasting glucose and body mass index among pregnant women without pre-existing diabetes with offspring being large for gestational age and preterm birth: a cohort study in China. *BMJ Open Diabetes Res Care*. 2021; 9(1): e001641.
9. Schjenken JE, Green ES, Overduin TS, Mah CY, Russell DL, Robertson SA. Endocrine Disruptor Compounds-A Cause of Impaired Immune Tolerance Driving Inflammatory Disorders of Pregnancy? *Front Endocrinol (Lausanne).* 2021; 12: 607539.
10. Tang W, Mao J, Li KT, Walker JS, Chou R, Fu R, Chen W, Darville T, Klausner J, Tucker JD. Pregnancy and fertility-related adverse outcomes associated with *Chlamydia trachomatis* infection: a global systematic review and meta-analysis. *Sex Transm Infect*. 2020; 96(5): 322-329.
11. Jaiswal N, Puri M, Agarwal K, Singh S, Yadav R, Tiwary N, Tayal P, Vats B. COVID-19 as an independent risk factor for subclinical placental dysfunction. *Eur J Obstet Gynecol Reprod Biol*. 2021; 259: 7-11.
12. Bouachba A, Allias F, Nadaud B, Massardier J, Mekki Y, Bouscambert Duchamp M, de la Fournière B, Huissoud C, Trecourt A, Collardeau-Frachon S. Placental lesions and SARS-Cov-2 infection: Diffuse placenta damage associated to poor fetal outcome. *Placenta*. 2021; 112: 97-104.