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The influence of selected risk factors on premature birth - statistical research

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Abstract

For a very long time, scientists have been interested in preterm births, which are an extremely interesting object of research, and are worth investigating in context of a vast number of new clinical applications. A number of factors may contribute to the early termination of pregnancy, including groups related to the conditions of mother's organism. In this work, it was examined whether environmental, maternal and fetal factors could affect normal time of birth. Variables that were considered to influence the length of prenatal development were categorized as biological, describing the state of mother's health and pregnancy, and those describing the socio-economic status of parents. The research material was subjected to exploratory analysis. For categorized variables, numerical tables were constructed, and for quantitative variables the basic measures of position and variability were presented (mean, minimum, maximum, standard deviation, median, quartile distribution). To analyze the differences in the frequency distributions of the examined variables, the $\chi 2$ tests were used. To estimate the duration of the pregnancy of the tested mothers, the survival analysis (the product limit method - Kaplan-Meier method) was applied. The analysis showed a statistically significant effect on the duration of pregnancy and the nature of its course, indicating a shortening of pregnancy in the presence of risk factors ($\chi 2=196,23$; df = 4; $p<0,001$). The course of the curves shows an increase in the frequency of premature delivery in the case of clinically diagnosed risk factors. This will certainly provide a strong basis for improving the care of premature newborns and minimizing the risk for the mother.

Running title: Statistics of premature birth factors of influence

Keywords: pregnancy, risk factors, statistical analysis, correlation, preterm birth

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Introduction

For a very long time, scientists have been interested in preterm births, which are an extremely interesting object of research and are worth investing in new and more developed applications than before. A significant improvement in the survival rate of newborns born prematurely, i.e. below 37 weeks of gestation, can be observed. This is most likely due to the advancements in clinical care covering the future mothers. Despite this, unfortunately, we still have to deal with a high percentage of pregnancies terminated prematurely. It has serious consequences, manifested as disease complications in newborns.

A number of factors may contribute to the early termination of pregnancy, including groups of factors related to the mother's body. Within them, one can distinguish maternal factors acting on the fetus in a direct way (distribution of backup materials, building materials, minerals, immune elements or oxygen, as well as harmful substances and pathogens) and indirectly acting factors (external environment in relation to the mother's body - the mother can transfer to the developing body both the benefits and costs of living in given environmental conditions) [1,2]

Studies on the influence of maternal factors on the length of prenatal development are closely related to the health conditions and conditions created by the parents' living environment [3]. The persistent high prenatal life burden is in large part due to the limited understanding of the mechanisms controlling the normal time of delivery in humans and how individual genetic variation and environmental exposure disrupt these mechanisms, causing preterm delivery [4].

When discussing preterm delivery, one would not be able to overlook the aspect of the common path of birth. It occurs the same for premature births and births of time. It is an algorithm of processes taking place in the mother's body, beginning with the implantation of the blastocyst in the endometrium, and having its final in the form of a child's birth, by which we understand the expulsion of the newborn from the mother's body in a natural or assisted way [5]. In terms of the common path of delivery, the difference between childbirth and premature delivery concerns a group of factors (general biological, disease, economic, social or cultural), through which the mechanism of a common labor path in preterm delivery is induced in a non-physiological way. In the case of delivery at the correct time, the activation of the common birth path occurs naturally (physiologically).

So far, 6 categories of most common risk factors for preterm labor have been identified: infectious, bearing, fetal, socio-economic, health and genetic factors [5,6]. They are presented in the **table 1**.

The main goal of these studies was to determine the correlation between the risk factors described and the premature uterine contractile function, which results in prematurely terminated pregnancy and spontaneous delivery. The significance of the correlation of the tested fetal factors with specific parameters of the perinatal state of cultural and socio-economic factors that characterize the indirect environment of descendants' development was estimated. The same applies to maternal factors that characterize the direct environment of offspring development.

Materials and methods

Research material

The research material was collected as part of an interdisciplinary project concerning the inter-individual diversification of perinatal maturity. It included 2018 newborns (1279 boys and 1139 girls) from single pregnancies, born alive at the Gynecological and Obstetrical Clinical Hospital of the Poznan University of Medical Sciences in Poznań and infants who were transferred to the hospital in the first days of their life. Data were obtained from patient maternity cards and neonatal discharge cards.

A newborn baby is considered alive when it completely leaves mother's body, either naturally or with assistance, regardless of the duration of pregnancy and when breathes and shows any signs of life (heart function, umbilical pulsation, or pronounced contractions of dependent muscles) by will [7].

It was examined whether environmental, maternal and fetal factors could affect the unprotected birth. Variables that were considered to influence the length of prenatal development: biological, describing the state of mother's health and pregnancy, and those describing the socio-economic status of parents of the examined child were chosen on the basis of comprehensive literature [1,8–11]:

- Biological variables: gender of the examined child, the age of the mother, order of pregnancy and delivery, occurrence of miscarriages
- Variables describing the state of mother's health (viral, bacterial and parasitic infections) and describing the course of pregnancy (disturbances in fetal waters, placental abnormalities, premature rupture of the membranes, thyroid hormonal disorders, pre-eclampsia, epilepsy, diabetes.) In addition (moreover?), a group of mothers with premature contractions was identified, in which the above-mentioned disorders were not diagnosed - clinically diagnosed disorders. Additionally, a group of mothers exhibiting premature cramps, that have not been caused by the above mentioned clinically diagnosed disorders, was also isolated.
- Variables describing the socio-economic status of the parents of the examined child: the urbanization degree of the place of residence

The research material collected during the experiment embraces a very wide range of data. To sys-

tematize it, the data was categorized in accordance with the requirements of statistical analyzes and is presented as follows:

Fetal age of the examined newborns (w.p. – the week of pregnancy)

- 24^{th} w.p. – fetal newborns
- 24^{th} – 28^{th} w.p. – newborns born as extremely immature
- 29^{th} – 32^{nd} w.p. – newborns born very prematurely
- 33^{rd} – 36^{th} w.p. – newborns born prematurely
- 37^{th} – 42^{nd} w.p. – newborns born at the time

Birth weight

- ≤500 g - fetal newborns
- 501-1000 g - extremely low body weight (ELBW)
- 1001-1500 g - very low birth weight (VLBM)
- 1501-2500 g - moderate birth weight (MBW)
- 2501-4500 g - appropriate birth weight (ABW)
- ≥4500 g – large body weight (LBW)

Birth weight in relation to fetal age

- <10 centile – small for gestational age (SGA)
- 10-90 centiles – appropriate for gestational age (AGA)
- > 90 centile – large for gestational age (LGA)

Mother's age

- Up to 19 years old
- 20-24 years old
- 25-29 years old
- 30-34 years old
- Over 35 years of age

The order of pregnancy and childbirth

- First
- Second
- Third
- Fourth and next

On the basis of information about the state of health of the mother and the fetus, normal and complicated pregnancies were distinguished. The final result provided five categories defining the nature of the pregnancy course as:

- Correct
- Complicated by the occurrence of premature uterine contraction
- Complicated by the occurrence of maternal risk factors
- Complicated by the presence of fetal risk factors
- Complicated by the co-occurrence of maternal and fetal risk factors

Urbanization degree of the place of residence:

- > 500 thousand residents
- 100 – 499 thousand residents
- 50 – 99 thousand residents
- 20 – 49 thousand residents
- 10 – 19 thousand residents
- <10 thousand residents and villages

Statistical analysis

The research material was subjected to exploratory analysis. For categorized variables, numerical tables were constructed, and for quantitative variables the basic measures of position and variability were presented (mean, minimum, maximum, standard deviation, median, quartile distribution). In order to analyze the differences in the frequency distributions of the examined variables, the $\chi 2$ tests were used.

To estimate the duration of the pregnancy of the tested mothers, the survival analysis (the product limit method - Kaplan-Meier method) was applied [12].

Statistical analyzes were carried out using the Statistica 13 program.

Ethical approval

The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee. The research was carried out with the permission of the Bioethical Commission at the Poznan University of Medical Sciences (No. 538/14).

Results

The research has been conducted on newborns born between the 20^{th} and 42^{nd} week of pregnancy ($\bar{x}$ = 38, Med = 39, SD = 3). The initial basis for the study was 2418 women, of whom 399 gave birth prematurely, i.e. before the 37^{th} week of pregnancy. It constituted 16.5% of all surveyed women. There were 1279 boys and 1139 girls among newborns. **Table 2** describes the incidence of births in particular categories of fetal age and sex.

The birth weight of newborn babies ranged from 390 g to 5070 g ($\bar{x}$ = 3211 ± 747 g, Med = 3340 g). For boys $\bar{x}$=3250±769 g; Me=3380 g; Min=390 g; Max=4990 g, while for girls $\bar{x}$=3167±720 g; Me=3280 g; Min=390 g; Max = 5070 g. According to the statistical data, 85% of newborns were born with normal body weight, i.e. 2501-4500 g. **Table 3** describes the frequency of births in relation to the sex of newborns and to the individual birth category of their body weight.

An analysis of the fetal age of newborns from the studied variables (clinical, biological and socio-economic) was performed. The calculations were made using the statistical test $\chi 2$ and the results are presented in **table 4**. The bolding of variables in the table means that they are statistically significant.

The analysis of the probability of the occurrence of labor in subsequent weeks of fetal age is presented in **figure 1**.

The analysis showed a statistically significant effect on the duration of pregnancy and the nature of its course, indicating a shortening of pregnancy in the presence of risk factors (χ^2=196,23; df = 4;

TABLE 1 Systemized risk factors for preterm delivery

Infectious factors	Bearing factors	Fetal factors	Socio-economic factors	Genetic factors	Health factors
-asymptomatic bacteriuria -urinary tract infections - abnormal bacterial flora of the vagina -intra-uterine infection -nephritis -periodontitis -inflammation of the vagina and / or cervix	-bearing abnormalities -leading bearing -premature -separation of the placenta -placental inflammation	-developmental defects -inhibition of intrauterine growth -intrauterine death	-absence or insufficient antenatal care -low level of education and income of parents -low socio-economic status -ethnicity -drugs (alcohol, narcotics, smoking) -mother's age	-single nucleotide polymorphism in genes considered as potentially involved in premature births -epigenetic modifications (DNA methylation and histone deacetylation) -extensive post-translational protein modifications -the diversity of alleles of genes considered as potentially involved in premature births	-multiple pregnancy -diabetes -bleeding from the genital tract in the second and third trimester of pregnancy -fibroids -hypertension -anemia -miscarriage in the second trimester -premature rupture of the membranes -uterine defects: uterus septum, bicornate

TABLE 2 Prevalence of births in particular categories of fetal age and sex

Fetal age (w.p.)	Total					
	N	%	Boys	%	Girls	%
<24	16	1	6	<1	10	<1
24-28	36	1	20	1	16	1
29-32	104	4	66	3	38	2
33-36	243	10	145	6	98	4
37-42	2019	84	1042	43	977	40

TABLE 3 The frequency of births in relation to sex and individual categories of birth weight

Birth weight (g)	Total					
	N	%	Boys	%	Girls	%
<500 g	7	<1	3	<1	4	<1
501 g – 1000 g	35	1,5	18	1	17	2
1001 g – 1500 g	66	3	39	3	27	2
1501 g – 2500 g	224	9	116	9	108	9
2501 g – 4500 g	2040	84	1072	84	969	85
>4500 g	42	2	29	2	12	1

TABLE 4 Differences in pregnancy duration depending on clinical, biological and socio-economic variables

Variable	x^2	df	p
Sex	12,10	4	0,02
Mother's age	32,77	16	0,0079
The order of pregnancy	80,67	32	0,00000
The order of delievery	71,95	28	0,00001
Miscarriages	24,43	24	0,44
Infections (viral, bacterial, parasitic)	17,93	4	0,0013
Thyroid disorders	34,12	12	0,00065
Diabetes	26,15	32	0,76
Disorders in the amount of fetal waters	26,36	12	0,0095
Bearing irregularities	141,61	20	0,00000
Premature rupture of the membranes	408,15	12	0,00000
Intrauterine hypoxia	11,97	4	0,018
Infection of the newborn	488,53	4	0,00000
Intrauterine pneumonia	204,71	4	0,00000
Defects of the heart and circulatory system	294,26	8	0,00000
Defects of the central nervous system	79,66	8	0,00000
Genetic defects	179,91	96	0,052
Morphological defects	75,79	8	0,00000
Defects of the respiratory system	35,54	4	0,00000
Disorders of the genitourinary system	23,17	8	0,0032
Disorders of the digestive system	29,78	4	0,00001
Metabolic defects	3,80	4	0,43
Degree of urbanization of the place of residence	51,58	24	0,0009

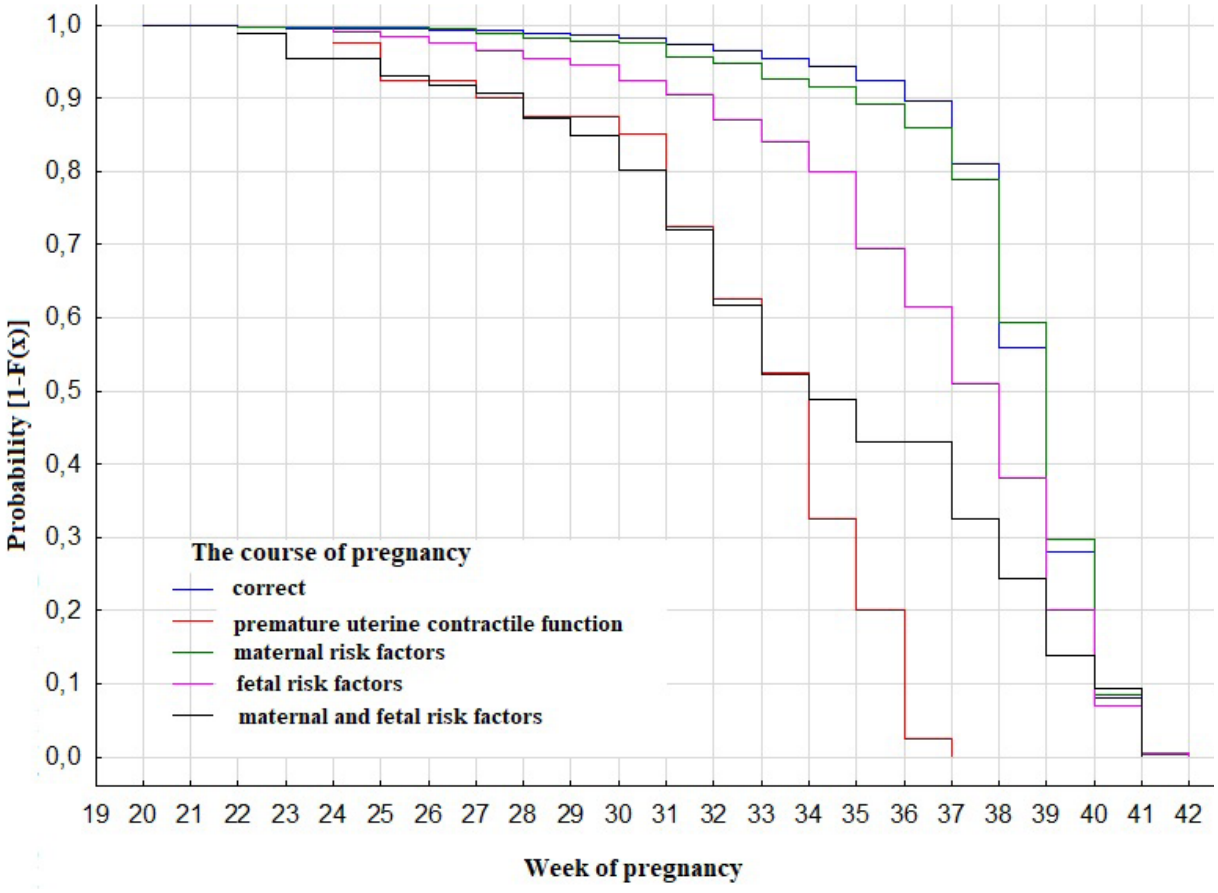

FIGURE 1 The probability of delivery in subsequent weeks of fetal age

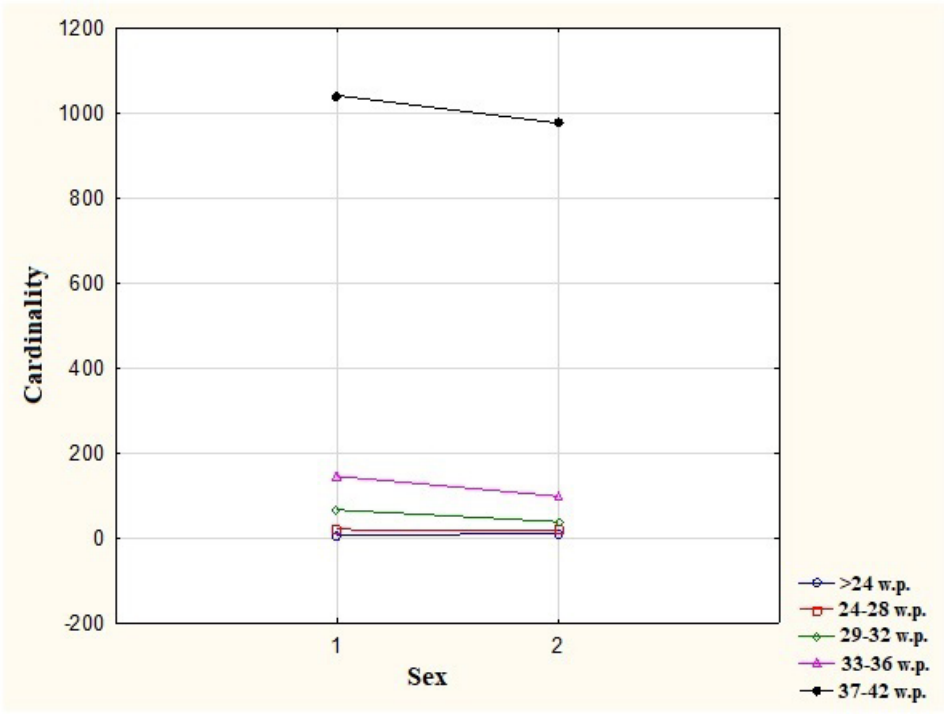

FIGURE 2 Graph of the relationship between the length of pregnancy and the sex of newborns; 1 - boys, 2 - girls

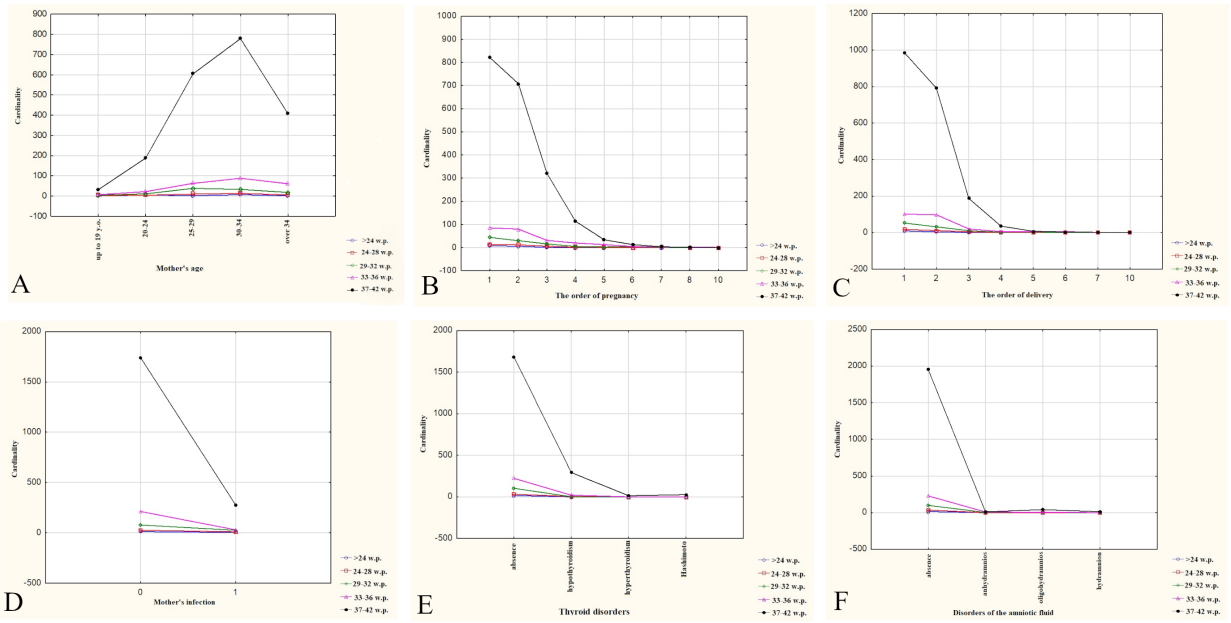

FIGURE 3 a) The dependence of pregnancy duration on the mother's age; b) The dependence of the duration of pregnancy on the order of pregnancy; c) The dependence of the length of pregnancy on the order of delivery d) The dependence of pregnancy duration on maternal infection; 1 - no infection, 2 - occurrence of infection; e) The dependence of pregnancy duration on thyroid function disorder; f) The dependence of the duration of pregnancy on disturbances in the amount of fetal waters

p<0,001). The course of the curves shows an increase in the frequency of premature delivery in the case of risk factors diagnosed clinically. The sharp drop in the curves in the early weeks of pregnancy is clearly visible in the case of maternal and fetal comorbidity, when exposed to fetal and maternal risk factors. In turn, the curve estimated for children born from pregnancies at risk of premature systolic activity does not show significant deviations from the curve estimated for children from normal pregnancy.

The graphs (**Fig. 2-5**) show the dependence of the duration of pregnancy on the sex of the child, mother's age, pregnancy sequence, birth order, mother's infection, newborn infection, thyroid disorders, disorders

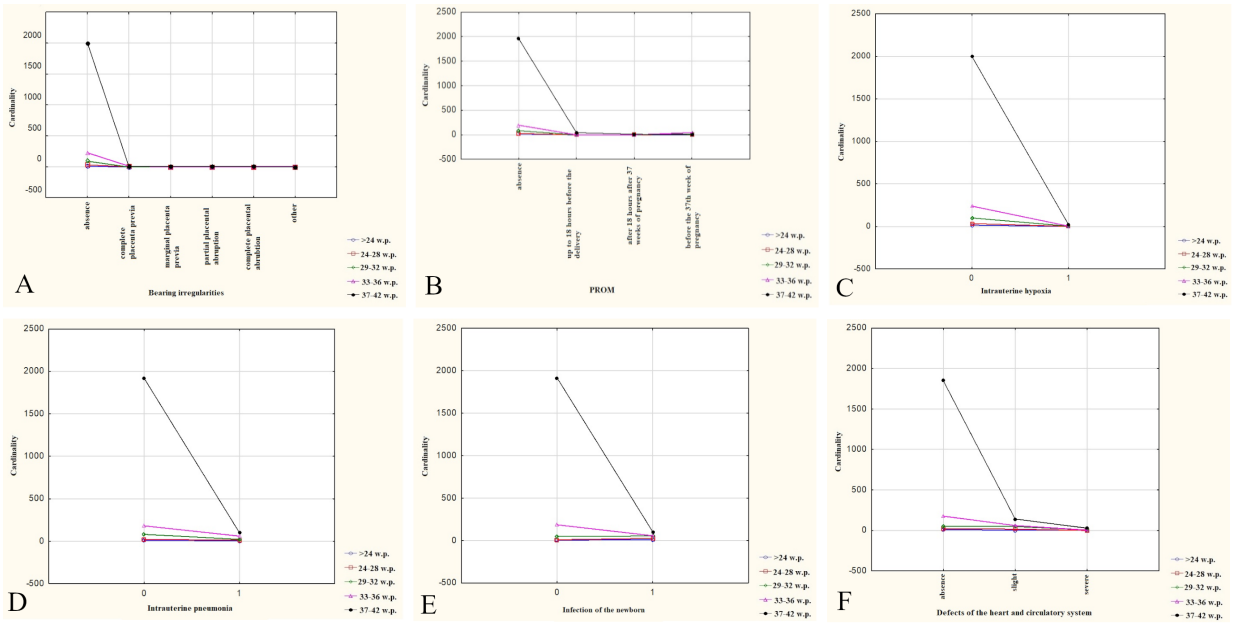

FIGURE 4 a) The dependence of pregnancy duration on bearing abnormalities; b) The dependence of pregnancy duration on premature rupture of membranes; c) The dependence of pregnancy duration on intrauterine hypoxia; 0 - non-occurrence of intrauterine hypoxia, 1 - occurrence of intrauterine hypoxia; d) The dependence of the duration of pregnancy on intrauterine pneumonia; 0 - non-occurrence of intrauterine pneumonia, 0 - occurrence of intrauterine pneumonia; e) The relationship between pregnancy duration and infection in the newborn; 0 - no infection, 1 - infection in the newborn; f) The dependence of the duration of pregnancy on the occurrence of cardiac and cardiovascular defects

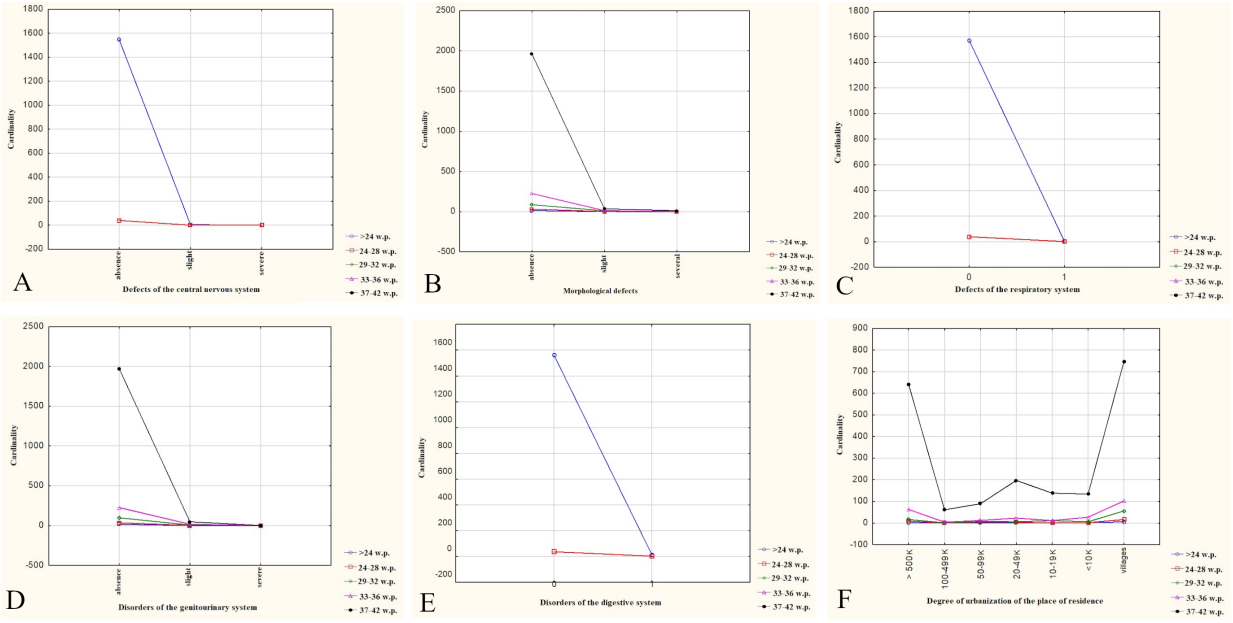

FIGURE 5 a) The dependence of pregnancy duration on the occurrence of central nervous system defects; b) The dependence of pregnancy duration on the occurrence of morphological defects; c) The dependence of the length of pregnancy on the occurrence of gastrointestinal defects; d) The dependence of the length of pregnancy on the occurrence of urogenital defects; e) The dependence of the length of pregnancy on the occurrence of gastrointestinal defects; f) The dependence of the duration of pregnancy on the urbanization degree of the place of residence

in the amount of fetal waters, placental abnormalities, PROM, intrauterine hypoxia, intrauterine pneumonia, heart defects and of the circulatory system, defects of the central nervous system, morphological defects, defects of the respiratory, genitourinary and digestive system and also on the degree of urbanization of the place of residence. All variables presented in the diagrams below are statistically significant.

TABLE 5 Impact of the studied variables on the occurrence of premature uterine contraction

Variable	x^2	df	P
Sex	8,32	1	0,0039
Mother's age	4,38	4	0,36
Gestational age	281,05	4	0,00001
The order of pregnancy	11,26	7	0,13
The order of delivery	13,25	6	0,04
Miscarriages	6,15	5	0,29
Infections (viral, bacterial, parasitic)	1,15	6	0,98
Thyroid disorders	2,51	3	0,47
Diabetes	10,86	8	0,21
Disorders in the amount of fetal waters	0,33	3	0,95
Premature rupture of membranes	13338,98	3	0,00001
Infection of the newborn	160,05	1	0,00001
Intrauterine pneumonia	208,54	1	0,00001
The occurrence of congenital defects			
Defects of the heart and circulatory system	22,45	1	0,00001
Defects of the central nervous system	38,87	2	0,00001
Genetic defects	12,13	13	0,52
Morphological defects	3,37	2	0,19
Defects of the respiratory system	11,82	1	0,00059
Disorders of the genitourinary system	0,093	2	0,95
Disorders of the digestive system	8,14	1	0,0043
Metabolic defects	0,025	1	0,87
Degree of urbanization of the place of residence	11,99	6	0,062

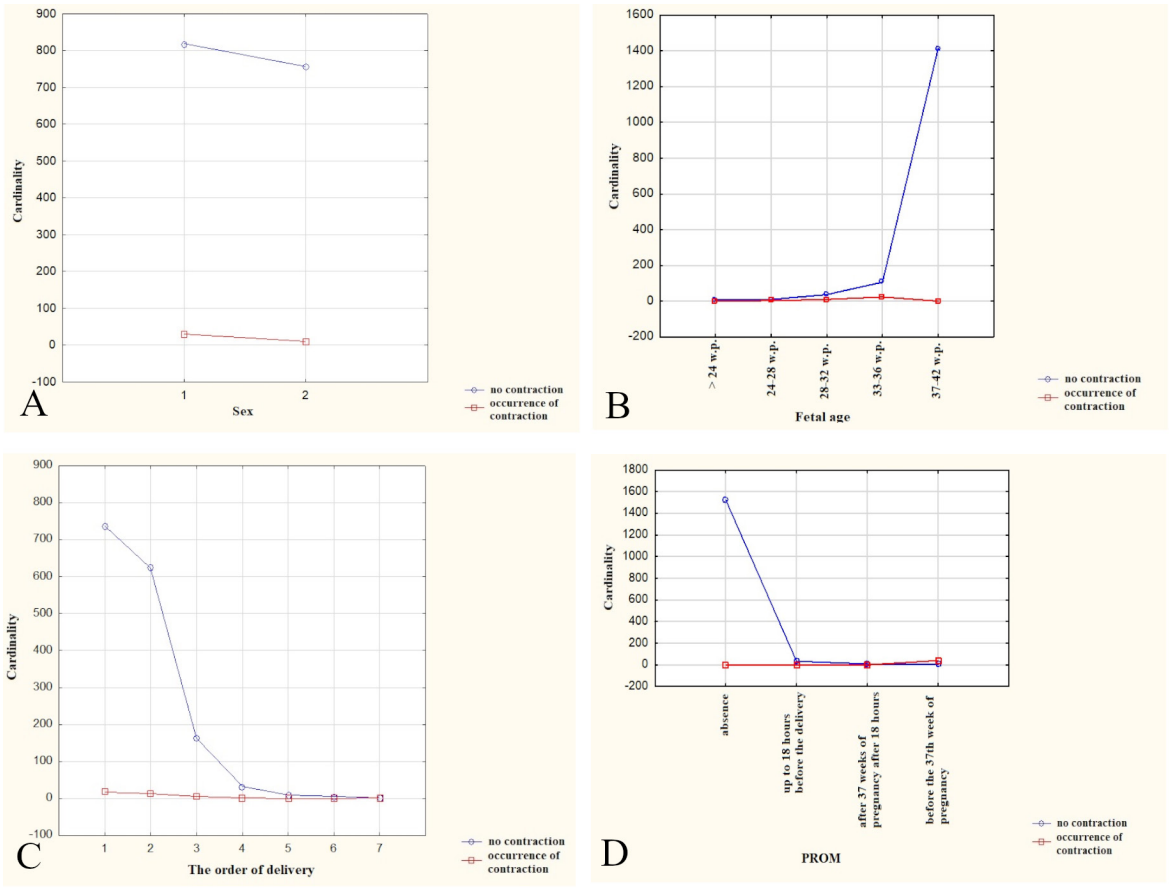

FIGURE 6 a) The dependence of the premature uterine contractile function on sex: 1 – boys, 2 – girls; b) The relationship between premature uterine contraction and fetal age; c) The dependence of the premature uterine contractility on the order of delivery; d) The dependence of the premature uterine contractile function on premature rupture of membranes

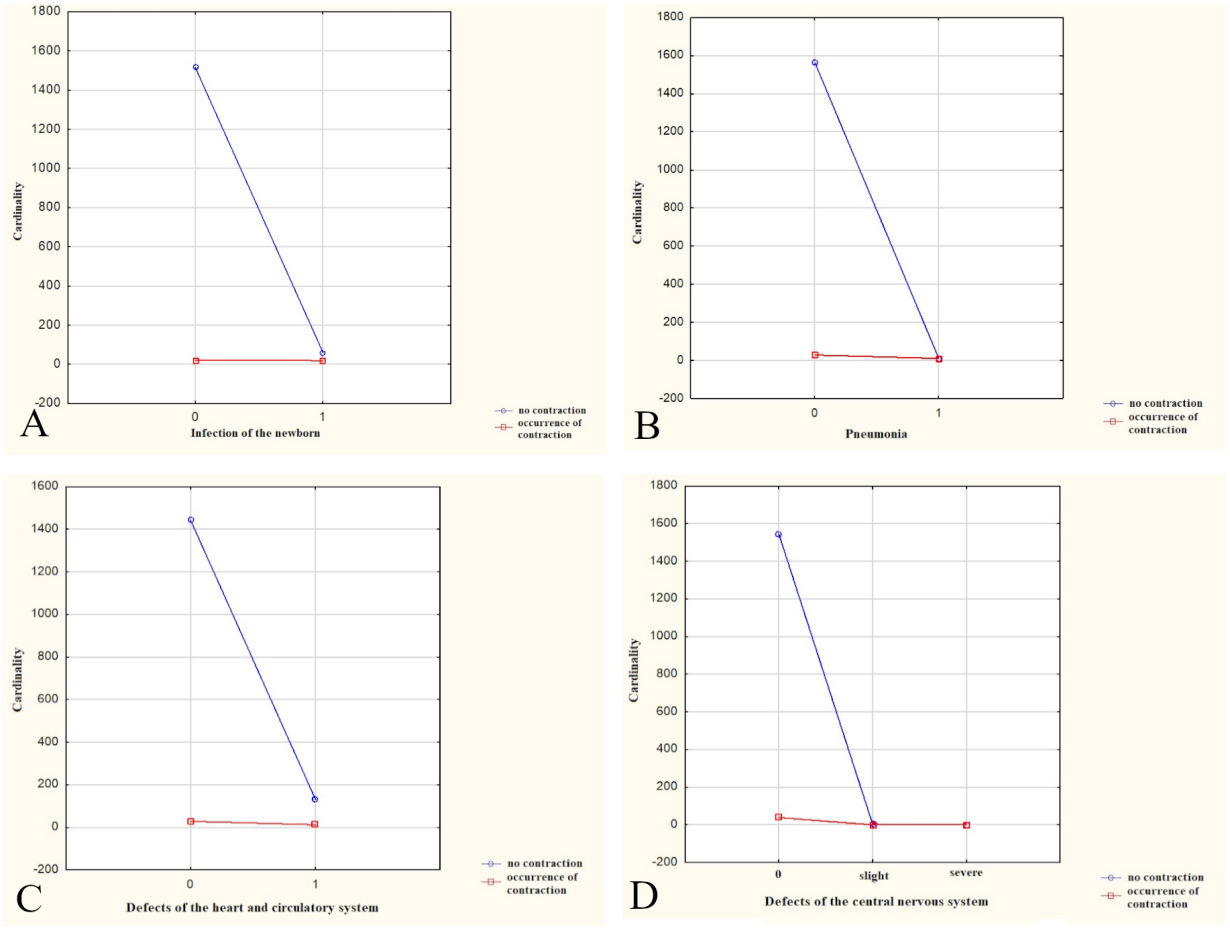

FIGURE 7 a) The dependence of the premature uterine contractile function on infection of the newborn: 0 - no infection, 1 - infection of the newborn; b)The dependence of the premature uterine contractile function on intrauterine pneumonia: 0 - non-occurrence of intrauterine pneumonia, 1 - occurrence of intrauterine pneumonia; c) The dependence of the premature uterine contractile function on the occurrence of cardiac and cardiovascular defects: 0 - no defects of the heart and circulatory system, 1 - occurrence of cardiac and cardiovascular defects; d) The dependence of the presence of premature uterine contractile function on the occurrence of defects of the central nervous system

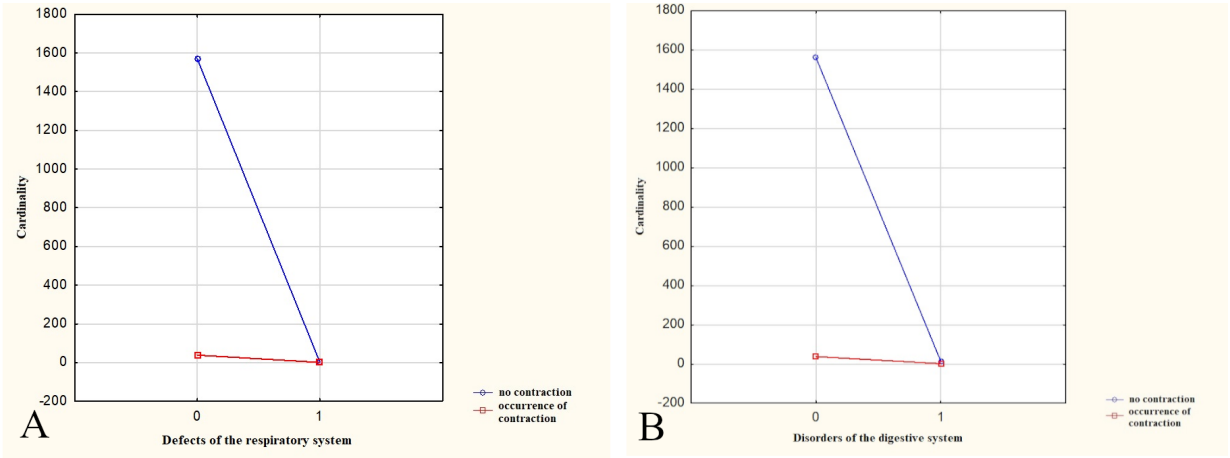

FIGURE 8 a) The dependence of the premature uterine contractile function on the occurrence of defects in the respiratory system: 0 - no defects of the respiratory system, 1 - defects of the respiratory system; b) The dependence of the premature uterine contractile function on the occurrence of gastrointestinal defects: 0 - the absence of gastrointestinal defects, 1 - occurrence of gastrointestinal defects

Subsequently, the relationship between selected risk factors and the occurrence of premature uterine contraction function was examined. The calculations were made using the statistical test $\chi 2$. The **table 5** shows the relationship between the occurrence of premature uterine contraction and the vari-

ables studied. The bolding of variables in the table below means that they are statistically significant.

The following graphs (**Fig. 6-8**) show the exact relationship between the selected variable and premature uterine contractile function. Only statistically significant results are presented here.

The graphs show that there is a statistically significant correlation between sex of the child, fetal age, birth order, PROM, newborn infection, intrauterine pneumonia, heart and circulatory system defects, central nervous system defects, respiratory system defects, gastrointestinal malformations and occurrence of premature uterine contractions.

Discussion

It has been proven in this paper that a number of factors, biological, general and socio-economic, have a significant influence on preterm labor. These factors are also regularly investigated by many other scientists. For example, the study on the relationship between socio-demographic factors, obstetric factors, health conditions, and use of medications and premature birth has recently been conducted. Women who gave birth prematurely were at more advanced age, had a habit of smoking and had lower socio-economic status. The previous history of stress and dissociative disorders, fears, obsessive-compulsive disorders, eating disorders and the history of antidepressant medication were also significant, as well as alcohol abuse and psychoactive substance abuse [13].

The statistical analysis presented in this research confirms the influence of socio-economic factors on premature birth ($p < 0.005$). In 2014, Saba W. Masho et al. carried out a research on the multilevel factors affecting preterm delivery in the urban environment in the United States in a group of black and white women. The results from both groups turned out to be very similar. The research showed that there was a statistically significant relationship between preterm delivery and education, maternal age and paternal presence. It has also been shown that the chances of preterm delivery were higher among black women who, for various reasons, received insufficient or average prenatal care. In addition, it was found that the chances of preterm delivery were higher among women who lived in the neighborhoods with medium or high poverty levels of residents compared to women living in housing estates with the lowest level of poverty [14]. A study of a similar nature was a study conducted in 2015 by X. Zhang on the Chinese population. Zhang et al. showed that several risk factors, such as lower family income (≤ 2000 RMB / month), maternal age ≥ 35 years old and lower educational level, can be attributed to premature delivery in Western China [15]. An interesting relationship was also presented by J.W. Collins Jr., who stated that the adverse results of premature birth were significantly related to the crime rate in geographically defined areas of the city [16].

Infection and health factors have also been proven to be significant in terms of terminating pregnancy too early. A common, obvious risk factor may be too low mother's weight before and during pregnancy. Researchers observing children in 2012-2016 at the Siriraj Hospital have proven that low mother weight is significant for preterm delivery. Lacking nutrients that are necessary for collagen production or lacking vitamins and antioxidants to preserve the strength of fetal membranes could lead to premature weakening and rupture of the fetal membranes. According to the research, carrying heavy objects increases intra-abdominal pressure and can also play a significant role in this condition [17]. In a review by J.C. Dunkelberg [18], a few large studies were collected that clearly indicated that mothers infected with HBV or HCV were at greater risk of premature rupture of membranes, which resulted in delivery before the expected date. In 1997, dr Mary Frances Cotch examined a group of pregnant women who were infected with protozoan *Trichomonas vaginalis*. Studies have shown that the probability of premature delivery, preterm delivery with low birth weight and premature rupture was significantly higher in infected women than in non-infected women [19].

In our study, no correlation was found between diabetes and prematurity. Despite this, there are studies showing exactly this relationship. The studies on increased probability of premature birth in women with gestational diabetes were conducted in Vienna in 2010, where in a retrospective cohort study, 187 pregnant women with diabetes and gestational diabetes were compared with a randomized, controlled group of 192 normoglycemic women. The study clearly showed a relationship between diabetes and gestational diabetes and premature birth ($p = 0.002$) [20]. Sae-Lin P et al. have come to very similar conclusions. They found that fetal macrosomia and polyhydramnios can lead tan o excessive extension of the fetal membranes and their premature rupture. Both fetal macrosomia and polyhydramnios are a frequent phenomenon observed during pregnancy complicated by diabetes mellitus. [17]

The data collected at the hospital in Danbury (USA) by a team led by Dr. C.M. Salafia, showed that there is also a relationship between placental changes and premature delivery. Their results suggested that three separate placental changes (i.e., umbilical-chorioamniotinis, necrosis and chronic salpingitis are associated with prematurity. All three changes may represent acute or chronic inflammatory processes that may be causally related to preterm delivery [21]. In our study, the influence of biological factors on premature birth was also confirmed ($p < 0.005$).

Not only do we have to look for the causes of premature births, but we also need to think about how we can predict them early. The aim of the research work of scientists from Zhejiang University School of Medicine was to create a prognostic model for premature birth in women after cervical conization and evaluation of its effectiveness. The examined group included women who were currently in the middle of pregnancy. Studies have clearly shown that a model based on the age and length of the cervix during pregnancy can effectively predict preterm delivery in pregnant women after cervical conization [22]. This gives hope to many women, due to a minimally invasive procedure, to obtain the necessary information about the risk of premature birth and to avoid many problems and complications.

The result of this work is the analysis of many seemingly unrelated factors, which together create a network of important relationships on which the increased risk of premature delivery is based. The rich statistical analysis visualized on many graphs proves that many biological, socio-economic and genetic factors can be involved in earlier delivery. These include: the state of urbanization of the mother's city of residence, fetal age, mother's age, sex of the child, order of pregnancy, complications during pregnancy, maternal infections, placental abnormalities, intrauterine and extrauterine infections, congenital defects of the circulatory system, respiratory system and digestive system and congenital metabolic defects in the child.

Premature contractions of the uterus leading to delivery before the appointed time are a topic that needs to be constantly expanded. By discovering the newer aspects of this common problem, one will be able to predict some of the complications associated with earlier births. This will certainly provide a strong basis for improving the care of premature babies and minimizing the risk for the mother. The whole research is also aimed at making people aware of how complicated the human body is and how much is still to be discovered.

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Conflict of interest
The authors declare they have no conflicts of interest.

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