Оцінка факторів ризику виникнення природжених вад розвитку серед новонароджених м. Львова та Львівської області за 2002 - 2021 рр. (частина I)

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Вступ. Частота народження дітей з природженими вадами розвитку (ПВР) за даними ВООЗ сягає 4–6 % від загальної кількості новонароджених.

Мета роботи – визначити ймовірні фактори ризику виникнення «модельних» ПВР у новонароджених.

Методи. Проведено збір та аналіз клініко-епідеміологічних і медико-статистичних даних з джерел первинної документації про дітей, які народились в 2002-2020 роках з ПВР методом «випадок-контроль», заповнюючи реєстраційні карти в пологових установах м. Львова та Львівської області.

Результати. Реєстр «модельних» ПВР у дітей, які народились в 2002-2020 роках у пологових закладах м. Львова та Львівської області методом «випадок – контроль», налічує 1211 карт на дітей з ПВР та 1204 карти на дітей з контрольної групи. У структурі «модельних» ПВР на перше місце вийшли ПВР і деформації кістково-м'язової системи – 272 (22.5%), друге місце посіли щілини губи та піднебіння –193 (15.9%), третє місце хромосомні аномалії – 174 (14.4%). Зі збільшенням порядкового номера вагітності, починаючи з четвертої, спостерігалась статистично значуща різниця народження дитини з ПВР ($p<0,05$). Виявлено статистично значущу різницю [OR=3.97; 95%CI: 1.97; 7.99] в анамнезі щодо відсотка мертвонароджень (3,2%) у матерів, які народили дитину з ПВР порівняно із жінками контрольної групи (0,8%). Відсоток патологічної структури плаценти у жінок обстеженої групи (32,8%) був більшим [OR=3.71; 95%CI:3.01; 4.56], ніж у жінок контрольної групи (16,8%).

Серед матерів обох груп не виявлено статистично значущої різниці щодо анемії та гестозе I та II половини вагітностей, інтервалу між вагітностями, кількості абортів і самовільних викиднів ($p>0,05$).

Висновки. Перспективи подальших досліджень у цьому напрямі полягають у визначенні внеску генетичного чинника у виникненні ПВР у кожного пацієнта з врахуванням генеалогічного анамнезу родини.

Ключові слова: новонароджені, вади розвитку, фактори ризику, Львівська область, Україна.

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Assessment of risk factors for development of birth defects among newborns in Lviv region in 2002-2020 (Part 1)

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Introduction. The frequency of children with birth defects (BD) according to the WHO reaches 4-6% of the total number of newborns.

Objectives. The purpose of this work was to determine the probable risk factors for "model" BDs in newborns.

Methods. Analysis of clinical-epidemiological and medical-statistic data from the primary documentation on newborns in 2002-2020 with BDs by the "case-control" method filling out registration cards in maternity hospitals of Lviv region was conducted.

Results. There were filled 1204 healthy newborns' cards and 1211 cards of newborns with BDs. In the structure of "model" BD, the deformations of the musculoskeletal system composed 272 (22.5%) cases, clefts of the lip and palate accounted for 193 (15.9%) cases, chromosomal abnormalities comprised 174 (14.4%) cases. We observed statistically significant risk ($p<0.05$) of BDs for newborns with increased numbers of pregnancies in mothers. There was a statistically significant difference [OR=3.97; 95%CI: 1.97; 7.99] in the medical history relative to stillbirths (3.2%) in mothers with BD newborns as compared to women in the control group (0.8%). The prevalence of pathological structure of the placenta in women of the study group (32.8%) was higher [OR=3.71; 95%CI:3.01; 4.56] than in those of the control group (16.8%).

Mothers of both groups showed no statistically significant difference in anemia, preeclampsia, the interval between pregnancies, and the number of abortions and miscarriages ($p> 0.05$).

Conclusions. Further research in this area should be directed to determine the contributions of genetic factors in BD occurrence, considering the genealogical history of each family.

Keywords: Newborns, birth defect, risk factors, Lviv region, Ukraine.

Introduction

Birth defects (BD) are a serious, current problem, as children's health is a resource for the future. The safety of their lives is important, both to their families and to the state. A child with BD can be born into any family. This issue is not limited to parents with complicated reproductive medical histories. Young, healthy parents with no bad habits and women with normal pregnancies are likewise susceptible. Worldwide, approximately 5% of all children are born with BD [1,2].

BD are the third leading cause of fetal mortality during pregnancy, childbirth, and the postpartum period [3].

Researchers have uncovered a preserved ancient Egyptian (more than five thousand years old) picture of a patient with chondrodysplasia. In the Babylonian cuneiform (3800-2000 BC), there is a table listing 62 descriptions of BD. The study of BD established itself as an independent science, teratology, in 1822 after French scientist Étienne Geoffroy Saint-Hilaire (G. Saint-Hilaire) used the experimental method of research to investigate the causes of BD [4].

According to the World Health Organization (WHO), the incidence of newborns with BD is 4–6 %. Furthermore, BD will manifest in 15% of children during the first five-ten years of life. Annually, about 2.7 million children worldwide die from BD. More than 60% of the reasons have not been identified. About 25% of anomalies are a result of combined effects of many minor genetic defects and environmental risk factors; 10-13% of anomalies are related to the environmental impact; only 12–25% of BD have a genetic component [5, 6]. BD is one of the main causes of ante- and intranatal fetal death and infant mortality [7]. The prevalence of BD, according to the European Registration of Congenital Anomalies and Twins (EUROCAT), varies over a wide range (10.3-32.3 per 1000 infants). In Ukraine, it affects 29 per 1000 infants [8].

Every year in Ukraine, about 12 thousand children are born with hereditary and congenital pathologies. Up to 20% of children with disabilities developed them as a consequence of BD. Additionally, almost every third stillborn child has this pathology [9].

Among all BDs, the most commonly diagnosed are "model" (synonyms: rough, obvious) BD, recommended for required registration by the EUROCAT [8]. These are persistent disorders of the structure and function that occur in utero due to fetal developmental disorders. The causes of congenital anomalies, counting multiple BD, in Ukraine include gene mutations (14-17%), chromosomal and genomic mutations (9-10%), unfavorable environmental factors and other hereditary factors (40-65%) [10].

The main aims of monitoring include studying the epidemiology of BD [11], assessing the effectiveness of prevention programs at the population level, and detecting and controlling new teratogenic environmental factors. The combination of genome sequencing and chromosome microarray analysis in all future monitoring programs will significantly improve the diagnosis of BD associated with genetic mechanisms [12, 13].

Objective: The purpose of this work was to determine the probable risk factors for "model" BD in newborns.

Materials and Methods

We collected and analyzed clinical, epidemiological, medical, and statistical data from primary records on children born in 2002-2020 with BD using the "case-control" method [14]. Doctors filled out registration cards in maternity hospitals in the city of Lviv and Lviv region.

Two groups of mothers were of particular interest: those who gave birth to a child with BD and those who gave birth to a healthy child. The "case-control" method was used to identify possible factors that may cause BD in the offspring when compared with mothers of healthy children (control group).

In each case of BD, a "Registration Card of the Child with BD" was filled out. To create a control group, a "Registration Card of the Healthy, Full-Term Child" was filled out for a healthy, full-term child of the same sex born concurrently with a child with BD (according to the "Genetic Monitoring Guidelines" approved by the Head of the Medical-Organizational Department of the Academy of Medical Sciences of Ukraine on May 17, 2002 and the

Head of the Department of Medical Care for Children and Mothers of the Ministry of Health of Ukraine on October 21, 2001) [15].

All data were collected with the informed consent of the mothers. Women of children with BD answered and asked questions because they wanted to understand the cause of the BD in their offspring. Mothers with healthy children also gave their consent, as they understood that answering the questionnaire could help future mothers identify risk factors that cause BD.

Following the recommendations of the European Registry, the study considered the following defects: anencephaly, spina bifida, encephalocele, hydrocephalia, anotia, microtia, cleft palate (without cleft lip), cleft lip (with or without cleft palate), esophageal atresia, rectal atresia, renal agenesis, reduction defects of extremities, polydactyly, omphalocele, gastroschisis, abdominal wall defects, diaphragmatic hernia, transposition of main vessels, hypoplastic left heart syndrome, Down syndrome, multiple BD, microcephaly, arinencephaly/holoprosencephaly, anophthalmia, microphthalmia, choanal atresia, atresia or stenosis of the small intestine, hypospadias, indeterminate sex, epispadias, exstrophy of the bladder, cystic kidney disease, trisomy 13, trisomy 18.

Inclusion criteria were all "model" BD in newborns. Exclusion criteria were newborns with BD that were not on the list of "model" BD; BD in stillbirths; women from other regions of Ukraine who gave birth to a child with BD in Lviv region maternity hospitals.

Results

During 2002-2020 in maternity hospitals in Lviv region, 1204 cards were filled out for healthy newborns and 1211 cards for newborns with BD. In 598 (49.4%) boys and 613 (50.6%) girls, cases of "model" BD were diagnosed. The control group included 592 (49.2%) boys and 612 (50.8%) girls. Isolated BD was found in 1,45 (86.3%) newborns, while 166 (13.7%) children were born with multiple BD.

BD in the examined group of 1,211 infants included 272 (22.5%) deformations of the musculoskeletal system, 193 (15.9%) cleft lips and palates, 174 (14.4%) chromosomal abnormalities, 159 (13.2%) genital BD, 138 system (11.4%) BD of the nervous system, 101 (8.3%) cases of multiple BD, 90 (7.4%) BD of the cardiovascular system, 54 (4.5%) BD of the digestive system, 16 (1.3%) BD of the urinary system, 9 (0.7%) BD of the eye, ear, and neck and 4 (0.3%) BD of respiratory organs.

In the examined groups, 50.2% of first, 24.4% of second, and 13.8% of third pregnancies resulted in newborns suffering from BD. These data did not demonstrate a significant deviation from the control group where 48.1% of cases were first pregnancies, 29.0% of cases were second pregnancies, and 12.3% of cases were third pregnancies ($p>0.05$). In the examined group, 1169 (96.5%) children were born as a result of singleton pregnancies, while 42 (3.5%) cases included multiple gestations. All 1,204 (100%) control group pregnancies were singleton.

In our study, with every subsequent pregnancy, we observed a statistically significant risk ($p<0.05$) of BD for the child. In the BD group, 5.8% of children were born from the fourth pregnancy, 3.0% of children were born from the fifth pregnancy, 1.3% of children were born from the sixth pregnancy, 1.1% of children were born from the seventh pregnancy, 0.3% of children were born from the eighth and tenth pregnancies. In the control group, 10.0% of children were born from the fourth pregnancy, 0.5% of children were born from the fifth pregnancy, and 0.1% of children were born from the sixth, seventh, ninth and eleventh pregnancies.

In many women of both groups, not every pregnancy ended in childbirth due to several reproductive causes (miscarriages, abortions, stillbirths). Therefore, the number of births was slightly lower than the number of pregnancies, but no significant difference was found between mothers of both groups ($p>0.05$).

When studying factors, we did not find a statistically significant difference ($p>0.05$) for the following criteria. Pregnancy was desirable in 95.3% of mothers in the study group and 96.4% of mothers in the control group; it was undesirable in 4.1% of mothers in the BD group and 2.8% of mothers in the control group. The interval between the latest pregnancies was 3.9 ± 3.0 years in the study group and 4.3 ± 2.8

years in the control group (p>0.05). In the BD group, the first pregnancy ended in abortion in 9.8% of cases; in the control group – in 9.0% of cases. In general, the studied group contained 14.1% of abortion cases, the control group contained 13.8% of such cases (p>0.05). According to the analyzed data, "Child Registration Cards" demonstrated that 96 (7.9%) pregnancies in the BD group ended in miscarriage, of which 90 (7.4%) cases were miscarriages of the first trimester. In the control group, miscarriage occurred in 85 (7.1%) cases, of which 80 (6.6%) cases happened during the first trimester. There was no significant difference (p>0.05).

According to the mother's medical history in the BD group, the offspring died under the age of five in 27 cases, which amounts to 2.2% of cases; 19 cases occurred in the control group, which equals 1.5% of cases (p>0.05). However, a higher number of stillbirths (39 cases or 3.2%) were noted in women of the BD group as compared to women in the control group (10 cases or 0.8%), which was a statistically significant difference (p<0.05). The risk of BD childbirth in women with stillbirths in reproductive anamnesis was 3.97 [OR=3.97; 95%CI: 1.97; 7.99].

We analyzed probable risk factors that could lead to the birth of a child with BD: anemia, preeclampsia in the first and second periods of pregnancy, and the structure of the placenta according to ultrasonographic data.

During pregnancy, anemia (Fig. 1) was present in 539 (44.5%) cases in the study group and 525 (43.6%) cases in the control group (p>0.05). Pregnancy passed without anemia in 548 (45.3%) mothers with BD children and 546 (45.3%) mothers with healthy children (p>0.05). The risk of childbirth with BD in women with maternal anemia was 1.02 [OR=1.02; 95%CI: 0.86; 1.22]. A comparison of anemia prevalence during pregnancy in the study and control groups is presented in Figure 1.

Preeclampsia in the first half of pregnancy (Fig. 2) was present in 329 (32.4%) cases of the study group and 384 (31.9%) cases of the control group (p>0.05). The risk of BD childbirth in women with preeclampsia in the first half of pregnancy was 1.08 [OR=1.08; 95%CI:0.90; 1.29]. Pregnancy passed without preeclampsia in 682 (56.3%) mothers who gave birth to children with BD and in 724 (60.1%) mothers with healthy children (p> 0.05).

Preeclampsia in the second half of the pregnancy (Fig. 3) occurred in 415 (34.3%) cases in the study group and 406 (33.7%) cases in the control group (p>0.05). Pregnancy in the second half occurred without preeclampsia in 649 (53.6%) cases among mothers with BD children and in 641 (53.2%) mothers with healthy children (p>0.05). The risk of BD childbirth in women with preeclampsia in the second half of pregnancy was 1.01 [OR=1.01; 95%CI: 0.84; 1.20].

As a result of ultrasound screening, we found that the first interval of ultrasonography in the study group was 17.5 ± 7.1 weeks, in the con-

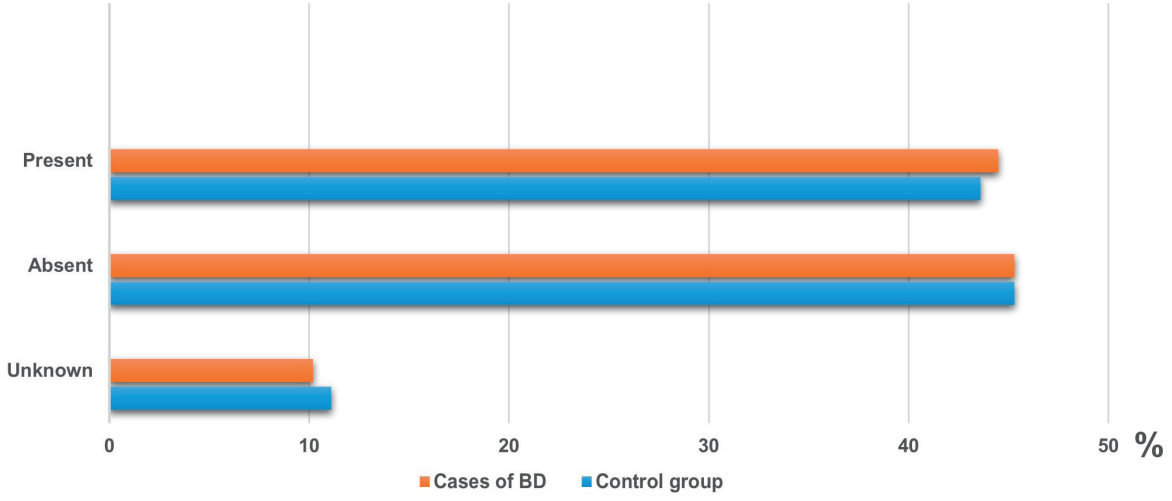

Figure 1. A comparison of anemia prevalence in pregnancies that resulted in newborns with BD and the control group

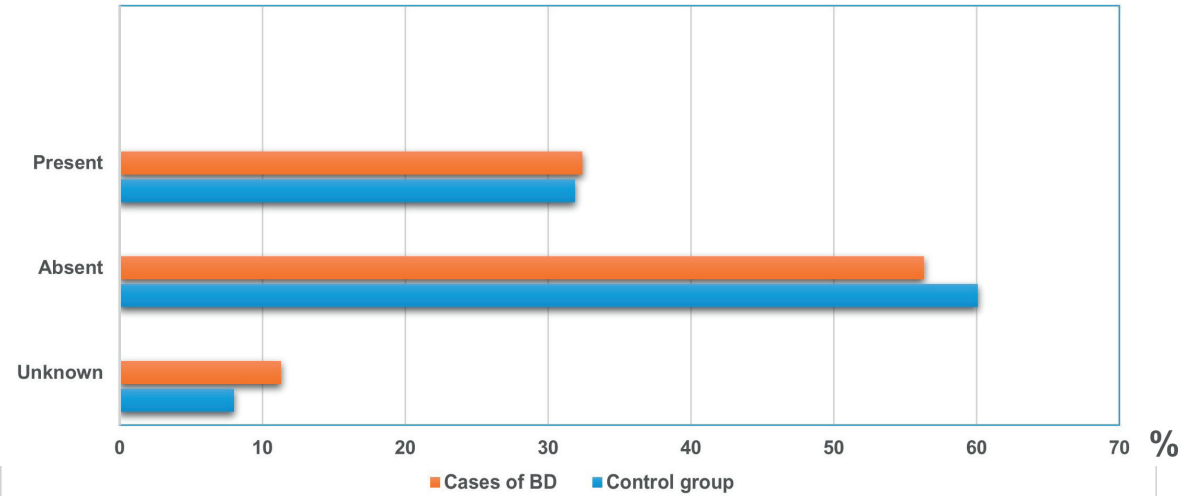

Figure 2. A comparison of preeclampsia prevalence in the first half of pregnancy in newborns with BD and the control group

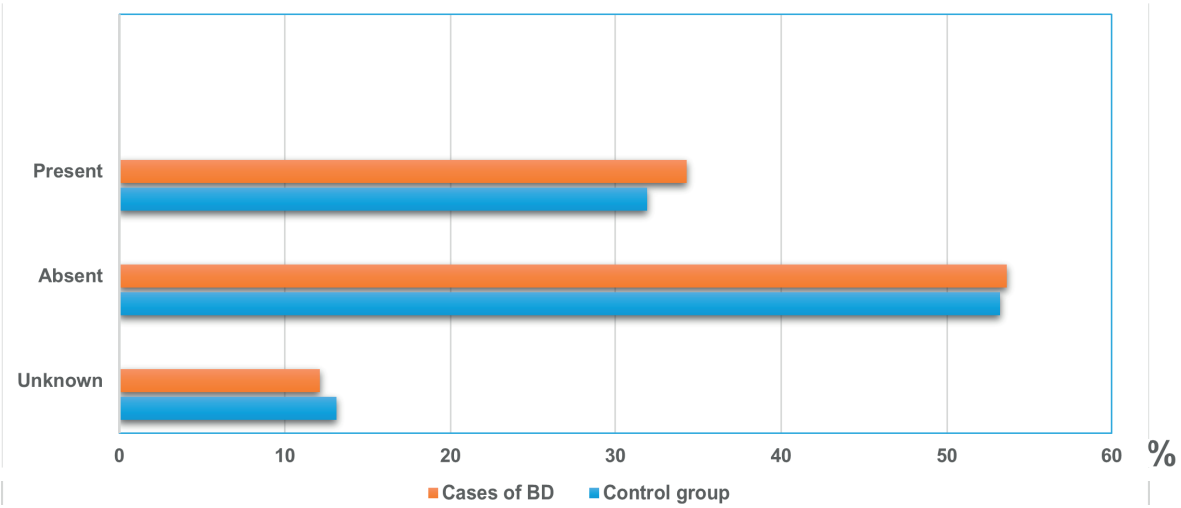

Figure 3. A comparison of preeclampsia prevalence in the second half of pregnancy in newborns with BD and the control group

trol group, it was 18.2 ± 8.1 weeks. The second ultrasonography in the BD group was performed on average at 24.5 ± 6.1 weeks, and in the control group – at 25.2 ± 6.6 weeks. Therefore, during the ultrasound examination of mothers in the study group, no statistically significant difference ($p>0.05$) was detected as compared to the control group. The ultrasound study was performed twice before the 28th week of pregnancy in 51.2% of cases of the BD group and 50.1% of cases of the control group ($p>0.05$).

Comparing the number of pathological childbirth cases in the BD group with the control group, we observed no statistically significant difference ($p>0.05$): pathological childbirth (cesarean section) occurred in 190 (15.7%) cases in the study group and 202 (16.8%) cases in the control group.

A comparison of the placental structure of the mothers in two groups is presented in Table 1.

The prevalence of pathological structure of the placenta in women of the study group was higher than in women of the control group, where $p<0.01$. The structure of the placenta was normal in 418 (34.5%) cases in the study group and 777 (64.6%) cases in the control group; pathological in 397 (32.8%) cases of the BD group and 199 (16.5%) cases in the control

Table 1

A comparison of the placental structure of newborns of the birth defect group and the control group

Placental structure	Cases of birth defect		Control group		Statistical significance
	n	%	n	%	P
Normal	418	34.5	777	64.6	<0.01
Pathological	397	32.8	199	16.5	<0.01
Unknown	396	32.7	228	18.9	<0.01
Total	1211	100	1204	100	

group; unknown in 396 (32.7%) cases of the BD group and 228 (18.9%) cases in the control group (p<0.01). The risk of BD childbirth in women with pathological placental structures was 3.71 [OR=3.71; 95%CI:3.01; 4.56].

Discussion

The "case-control" method is important to the epidemiological study of public health [16]. Data analysis is performed retrospectively, as the relationship between impact and outcome is studied by comparing individuals with pathology (in this article, "model" malformations in newborns) and those without it (control group – healthy newborns) [17]. Case-control studies are analytical because they are used to determine the causes and probable relationships between risk factors and the occurrence of BD in newborns.

The EUROCAT provides important epidemiological information and monitors this pathology in Europe, where information is mainly collected during the first year of the child's life [18]. According to the EUROCAT data for 2013-2019, defects of the cardiovascular system were ranked first, chromosomal abnormalities were ranked second, limb anomalies were ranked third, and urinary system defects were ranked fourth [19].

An analysis of the structure of BD in Odesa region (Ukraine) in 2008-2012 showed the annual predominance of cardiovascular, urinary, and musculoskeletal BD. Central nervous and digestive systems BD were ranked fourth and fifth in different years, except in 2009, when multiple BDs were ranked fourth (10.1 per 100,000 newborns) [20].

In our study, chromosomal abnormalities were among the three most common "model" BD in newborns. At the same time, cleft lips and palates, which were ranked second in our study, ranked eighth in 2013-2019 according to the EUROCAT – 14.51 per 10,000 newborns. It should be noted, that the BD spectrum in our study is characteristic for newborns, and differs from the BD spectrum in children aged 1 and older because at this age, the clinical picture of certain pathologies is much clearer. In the maternity hospital, attention is often paid to "model" BD that are diagnosed in the first days after birth or require surgical intervention – heart disease, anus atresia, esophageal atresia, polydactyly, etc.

According to Brazilian doctors [21], in 2013-2014, the prevalence of BD in 46,705 newborns was 1.04%. The musculoskeletal system BD were ranked first (42.1%), which was comparable to the data collected during our study. Although the prevalence of genital BD was almost the same – 11.6% (Brazilian study) and 13.2% (our study), in Brazil, they ranked second and in Lviv region, they ranked fourth.

Researchers from the United States found that among 289,365 surveyed newborns in Boston (USA), 5,941 (2.05%) children were diagnosed with one BD, sometimes, multiple BD. It was noted, that when obstetricians examined a newborn, most often they diagnosed visible external abnormalities, such as heart defects, undescended testicles, inguinal hernias, peripheral vascular abnormalities, and some internal abnormalities [22]. In 1990-2009, American scientists detected 873 (1.3%) cases of births with "isolated model" BD among 65,308 singleton pregnancies [23].

According to observations [14], among 465 stillbirths, 23.4% of cases had one or more serious anomalies as compared to 1,871 live births, where BD was diagnosed in 4.3%.

Reproductive anamnesis is very important to every pregnancy [24]. In the reproductive anamnesis of the mother, stillbirths belong to the many significant factors. Thus, according to the data collected on 73,337 newborns by scientists from the Netherlands [25] in 1998-2011, perinatal mortality associated with congenital anomalies was 1.27 per 1,000 births (95% confidence interval, 1.23-1.31), and the average stillbirth rate was 2.68% (range 0% -51.2%). According to German doctors, stillbirths ($p = 0.035$) were significantly more common among mothers who gave birth to a child with anorectal malformations as compared to the control group [26]. In our study, cases of stillbirths were observed in 3.2% of cases in the BD group and 0.8% of cases in the control group ($p<0.05$). We assume that stillbirths remain one of the important factors in a woman's reproductive history, which can lead to BD in future pregnancies.

Moreover, we have found that an increase in the ordinal number of pregnancies induces a statistically significant difference in the birth of a child with BD. In our opinion, with each subsequent pregnancy, less and less attention is paid to the woman's reproductive health, especially if previous pregnancies were uncomplicated and healthy children were born.

There are many doctors' reports about the significance of anemia as the probable risk factor for BD.

Anemia is very common in pregnant women, which significantly contributes to the deterioration of the mother's and her unborn child's health [27]. The sample of the study in the Democratic Republic of Congo included 412 women; 220 (53.4%) of them were diagnosed with anemia [28]. Anemia is associated with malaria, urinary system infections, cesarean section, prematurity, miscarriage, and stillbirth, with a 1.6-6.1-fold increased risk. We found no significant difference in the incidence of anemia among mothers in both groups (43.6% cases in the control group and 44.5% cases in the BD group). Our data on the effects of anemia is consistent with the data of Irish scientists [29], who note that anemia does not influence the course of pregnancy.

To study the potential risk between preeclampsia and individual BD, researchers in the United States analyzed data on 2,499,536 live births in California from 2007 to 2011. The risk of developing BD among the offspring of women with hypertension was only 1.37 times higher than in women without hypertension. The risk of BD was higher among offsprings of women with hypertension and diabetic disorders as compared to women, who did not have such pathology (relative risk ranged from 1.80 to 6.22). These findings supported a connection between preeclampsia and some BD, including spina bifida and cleft lip [30]. In contrast to this research, our study established no significant difference in preeclampsia in the first and second halves of pregnancy and the occurrence of BD in the offspring.

The placenta is very important in the development of the fetus; it attaches to the uterine wall and facilitates metabolism between the fetus and the mother. The placenta helps nourish the fetus and carries many functions necessary for its development [31]. Researchers who studied the connection between placental abruption and major BD in singleton births in Finland have found that placental abruption is associated with a nearly 1.6-fold increase in the risk of serious congenital malformations in the offspring [32]. In our study, in mothers of BD groups, the pathological structure of the placenta was almost twice as often as in mothers in the control group, which demonstrated the important role of placenta in assessing the viability of the fetus and newborn.

Monitoring BD is an important prevention program, that can be used to identify areas with an increased incidence of BD. Thus, it is possible to control environmental factors with teratogenic properties leading to BD in newborns who have been exposed to them during fetal development.

It can be concluded that the register of "model" BD in newborns in maternity hospitals in Lviv region was created using the "case-control" method during 2002-2020, which included 1,211 cards for newborns with BD and 1,204 cards for newborns of the control group. In the structure of the "model" BD, deformations of the musculoskeletal system composed 272 (22.5%) cases, clefts of the lip and palate accounted for 193 (15.9%) cases, and chromosomal abnormalities comprised 174 (14.4%) cases.

We observed a statistically significant risk ($p<0.05$) of BD for newborns with increased numbers of pregnancies in mothers.

There was a statistically significant difference ($p<0.05$) in the medical history relative to the percentage of stillbirths (3.2%) in mothers with BD newborns as compared to women in the control group (0.8%). The risk of BD childbirth in women with stillbirths in reproductive anamnesis was 3.97 [OR=3.97; 95%CI: 1.97; 7.99].

The prevalence of pathological structure of the placenta in women of the study group (32.8%) was higher than in women of the control group (16.8%), where $p<0.01$. The risk of BD childbirth in women with pathological placental structure was 3.71 [OR=3.71; 95%CI:3.01; 4.56].

Mothers of both groups showed no statistically significant difference in anemia, preeclampsia in the first and second halves of pregnancies, the interval between pregnancies, the number of abortions and miscarriages ($p>0.05$).

The main efforts should be aimed at preventing the development of BD in newborns. Monitoring birth defects plays an important role in medical practice. Further research in this area should be directed to determine the contribution of genetic factors to BD occurrence in each patient, taking into account the genealogical history of the family.

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