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The influence of risk factors on the development of birth defects among newborns in Lviv region (Ukraine) in 2002–2022 (Part 2)

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Introduction. Birth defects (BDs) are an essential public health issue in children; the identification of probable risk factors should be a priority for the healthcare system.

Objectives: This study aimed to determine the probable risk factors for “model” BDs in newborns.

Methods. We collected and analyzed clinical-epidemiological and medical-statistic data from the primary records of children with BDs born in 2002–2022 using the “case-control” method, filling out the registration cards in maternity hospitals of Lviv Region (Ukraine).

Results. There were 1,279 healthy newborns’ cards and 1,286 cards of newborns with BDs filled out. No significant difference was found in terms of body weight, height, head circumference, and chest circumference ($p > 0.05$) among children with BDs and the control group. The age of mothers with children affected by BD was 27.3 ± 6.1 years and had no statistically significant difference from the age of mothers of children in the control group - 25.6 ± 7.2 years ($p > 0.05$).

Mothers who gave birth to children with BDs used drugs in the preconception period [OR=2.46; 95% CI: 1.75; 3.44] and the first trimester of pregnancy [OR=4.76; 95% CI: 3.18; 7.14] significantly more often ($p < 0.05$) compared to mothers in the control group. Pre-pregnancy preparations were adequately conducted by 278 (21.6%) women who gave birth to children with BDs, which was statistically different from 563 (44%) women in the control group ($p < 0.05$) [OR=2.85; 95% CI: 2.39; 3.39].

Conclusions. More efforts are necessary to identify drug safety issues during pregnancy and to improve the current information system for clinical practice.

Keywords: newborns, birth defect, risk factors, age of mothers, anthropometric indicators, drugs, Lviv Region, Ukraine

Introduction

Birth defects (BDs) affect 3% of all children and are among the leading causes of child mortality. It was found that several maternal and environmental factors are significantly correlated with the occurrence of BDs [1–4]. There is a close relationship between BDs and folic acid deficiency, maternal age, medication use, etc. Certain medications, including folic acid antagonists and anticonvulsants, have been associated with various BDs [5]. It is known that maternal intake of folic acid before and during the first months of pregnancy reduces the risk of neural tube defects in an offspring [6,7].

According to current research, the mother's age can affect the occurrence of BDs in the child. With increasing age, the risk of adverse maternal and perinatal outcomes increases for women over 40 years of age [8–12]. Doctors from Taiwan note that maternal age (under 18 or over 30), prematurity, and low birth weight are associated with BDs in the child [13]. Scientists report on anthropometry indicators among newborns with BDs and healthy babies [14,15].

Since BD is a significant public health issue, identifying probable risk factors should be a priority for public policy and the healthcare system, as it would facilitate the development of an effective primary prevention strategy [16]. Identifying the risk of exposure to harmful factors is extremely important since some forms of BDs can be largely prevented if exposure to risk factors is reduced before and during pregnancy [17].

Objective: this study aimed to determine the probable risk factors for “model” BDs in newborns.

Materials and Methods

We collected and analyzed clinical-epidemiological and medical-statistic data from the primary records of children with BDs born in 2002–2022 using the “case-control” method [18,19]. Doctors filled out registration cards in maternity hospitals in the city of Lviv and Lviv Region (Ukraine).

The case-control study was designed to help determine whether exposure to specific factors is associated with BDs in an offspring. The study group consisted of mothers in maternity hospitals who gave birth to a child with BD, and the control group included women who gave birth to a healthy child. A case-control study design allows for multiple risk factors to be considered simultaneously. It is inexpensive, effective, and often less time-consuming to perform [18]. Thus, the study examined the weight, sex, and anthropometric data of the child at birth, the mother's age, the use of medication before and during pregnancy, pregnancy planning, etc.

In each case of BD, a “Registration Card of a Child with BD” was filled out. To create a control group, a “Registration Card of a Healthy, Full-Term Child” was filled out for a healthy, full-term child of the same sex born concurrently with a child with BD [18]. All data were collected with the mother's informed consent.

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 the extremities, polydactyly, omphalocele, gastroschisis, abdominal wall defects, diaphragmatic hernia, transposition of the main vessels, hypoplastic left heart syndrome, Down syndrome, multiple BDs, 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 aforementioned “model” BDs in newborns. Exclusion criteria were BDs in stillbirths; newborns with BDs that were not on the list of “model” BDs; women from other regions of Ukraine who gave birth to a child with BD in Lviv Region maternity hospitals.

The obtained data were standardized according to the Tenth Revision of the International Classification of Diseases (ICD – 10) and processed using the variational statistics method, the “Statistica 5” software package, and Microsoft Excel 2000: the study considered the arithmetic mean value (M), deviations from the arithmetic mean value (m), the odds ratio (OR), the confidence interval of the odds ratio (Exp), and p – the value of statistical significance [20].

The odds ratio was calculated using the following formula:

OR = ad/bc, where

a – the number of cases in the BD group;

b – the absence of cases in the BD group;

c – the number of cases in the control group;

d - the absence of cases in the control group.

The confidence interval of the odds ratio was determined using the following formula:

Exp (ln [(a + 0,5) (d + 0,5) / (b + 0,5) (c + 0,5)] + tσ),

t = 1,96; σ² = (a + b) (c + d) / (a + b + c + d) (a + b + c + d - 1).

Results

In the Lviv Region Maternity Hospitals, 1,286 cards were filled out for newborns with BDs and 1,279 – for healthy newborns in 2002–2022. Cases of “model” BDs were diagnosed in 647 (50.3%) girls and 639 (49.7%) boys. The control group included 648 (50.7%) girls and 631 (49.3%) boys.

BDs in the study group of 1,286 infants included: 292 (22.7%) cases of BDs and deformations of the musculoskeletal system, 212 (16.5%) cleft lips and palate BDs, 186 (14.5%) chromosomal anomalies, 176 (13.7%) BDs of the genital organs, and 142 (11%) BDs of the nervous system. Multiple BDs were diagnosed in 106 (8.2%) newborns during this period. In these 21 years, some BDs were diagnosed in isolated cases. Specifically, BDs of the urinary system were diagnosed in 20 (1.6%) cases, BDs of the eye, ear, and neck – in 10 (0.8%) cases, and BDs of the respiratory system – in 4 (0.3%) cases. Within the first hours after birth, 95 (7.4%) children were diagnosed with BDs of the circulatory system and 60 (4.7%) – with BDs of digestive organs. Previously, we reported the spectrum of BDs among newborns in Lviv Region between 2002 and 2020 [21]. The ranking of the spectrum of BDs among newborns between 2002 and 2022 was the same as between 2002 and 2020.

When comparing the anthropometric indicators of children with BDs and the control group, no significant difference was found (Table 1) in terms of body weight, height, head circumference, and chest circumference (p>0.05). The average value of body weight at birth for boys with BDs was 3,167.8 ± 512.1 g, for girls – 2,989.4 ± 628.9 g, in the control group – 3,324.1 ± 371.7 g and 3,291.3 ± 378.1 g, respectively (p>0.05). Height in the group of children with BDs among boys was 52.4 ± 2.6 cm, among girls - 49.9 ± 3.4 cm, but no significant difference (p>0.05) was found when comparing this indicator with the control group: 52.5 ± 1.7 cm in boys and 51.8 ± 1.6 cm in girls. There was also no statistically significant difference in head and chest circumference (p>0.05) among children with BDs and the control group.

Table 1

Comparison of anthropometric indicators of children with birth defects

Sign	Sex	Newborns with BDs (M±m)	Control group (M±m)	Statistical significance
Body weight, g	Boys	3167.8±512.1	3324.1±371.7	p>0.05
	Girls	2989.4±628.9	3291.3±378.1	p>0.05
Height, cm	Boys	52.4±2.6	52.5±1.7	p>0.05
	Girls	49.9±3.4	51.8±1.6	p>0.05
Head circumference, cm	Boys	33.6±2.3	34.4±1.4	p>0.05
	Girls	33.1±2.3	33.9±1.5	p>0.05
Chest circumference, cm	Boys	32.6±2.2	33.3±1.2	p>0.05
	Girls	32.4±2.6	33.4±1.4	p>0.05

Notes: M - the average value, m - the deviation from the average value

Head circumference at birth in boys with BDs was 33.6 ± 2.3 cm, in girls - 33.1 ± 2.3 cm; in the control group – 34.4 ± 1.4 cm and 33.9 ± 1.5 cm, respectively ($p > 0.05$). Chest circumference in the group of children with BDs was 32.6 ± 2.2 cm for boys, 32.4 ± 2.6 cm for girls, 33.3 ± 1.2 cm for boys in the control group, and 33.4 ± 1.4 cm for girls ($p > 0.05$).

Rh conflict was present in 36 (2.8%) cases of the study group and 29 (2.3%) cases of the control group ($p > 0.05$) [OR=1.24; 95% CI: 0.76; 2.04].

The age of mothers with children affected by BD was 27.3 ± 6.1 and had no statistically significant difference from the age of mothers in the control group – 25.6 ± 7.2 ($p > 0.05$). Table 2 shows cases of age distribution of mothers with children affected by BD and those in the control group.

Table 2

Age distribution of mothers with children affected by birth defects and the control group

Age, years	Cases of birth defects		Control group		Statistical significance
	n	%	n	%	p
<20	251	19.5	161	12.6	>0.05
20-24	404	31.4	382	29.9	>0.05
25-29	284	22.1	359	28.0	>0.05
30-35	167	13.0	215	16.8	>0.05
>35	180	14.0	162	12.7	>0.05
Total	1,286	27.3 ± 6.1	1,279	25.6 ± 7.2	>0.05

Although the proportion of mothers in the BD group was higher among persons younger than 20 – 19.5% and 12.6% in the control group, and among pregnant women older than 35 – 14.0% in the BD group and 12.7% in the control group, no significant difference was found between the mothers of both groups ($p > 0.05$).

Medication in the preconception period was used significantly more often ($p < 0.05$) by women from the study group – 119 (9.3%) women as compared to women from the control group – 51 (4%) cases [OR=2.46; 95% CI: 1.75; 3.44].

During the survey, a significant difference ($p < 0.05$) was established in medication usage before the 12th week of pregnancy among women of both groups – 132 (10.3%) versus 30 (2.3%). Women who subsequently gave birth to a child with BD used medication before the 12th week of pregnancy 4.76 times more often than women who gave birth to a healthy child [OR=4.76; 95% CI: 3.18; 7.14].

Pre-pregnancy preparations (tests for TORCH infections, thyroid hormones, prolactin, use of folic acid, and vitamins) were adequately completed by 278 (21.6%) women who gave birth to children with BDs, which was statistically different from 563 (44%) women in the control group ($p < 0.05$). Women in the control group planned their pregnancy 2.85 times more often than women who gave birth to a child with BD [OR=2.85; 95% CI: 2.39; 3.39].

Discussion and Conclusions

Infant birth weight is an important outcome of a healthy pregnancy, reflecting fetal and maternal health, closely related to perinatal mortality and morbidity; likewise, it influences the subsequent health of an individual. Argentinian doctors found that the weight of a child at birth and other factors were strongly determined by the topography of the province and climatic fluctuations in relation to its location within the Andes [22].

Sudanese doctors [23] noted that newborns with congenital heart defects were more often born with low weight than children without pathologies. However, no statistically significant relationship was found between the degree of birth weight and specific types of hemodynamic disorders.

In the present study, when comparing the anthropometric indicators of children with BDs and the control group, no significant difference was found in terms of body weight, height, head circumference, and chest circumference.

Maternal age of 35 years and older is usually considered advanced and often associated with various complications for the mother during pregnancy and for the child after birth [24]. The number of pregnancies in the advanced maternal age has been steadily increasing for decades. Women worldwide are postponing childbearing until a later age in both low-income and high-income countries [25].

On the other hand, many women give birth at a more advanced age for various reasons, including late marriage, infertility treatment, career and higher education, and the use of birth control methods. In developed countries, there is a tendency to give birth for the first time at the age of over 35, while in developing countries, a woman may have already given birth several times at the same age. This phenomenon can be explained by inefficient family planning methods, poverty, and a cultural preference for having large families [25].

According to a study by doctors from South America, the risk and severity of BDs increased with the mother's age [9]. They studied the database of newborns in Chile between 2001 and 2010, created by the Latin American Collaborative Study of Congenital Malformations (ECLAMC). For each newborn affected by the BD, the next healthy newborn of the same sex was registered and included in the control group. The study sample included 22,039 newborns: in particular, 11,024 cases of children with BDs and 11,015 healthy children. The same data were observed by doctors in Santiago (Chile) [26], where the average age of the mother was higher in cases where children were born with BDs compared to the control group ($p=0.0149$).

Nevertheless, in many countries around the world, in particular in Saudi Arabia and other countries of the Middle East, women still give birth to children after the age of 35 due to the solid financial status of their husbands, where the man is the primary breadwinner, and desire to have a large family [27]. For instance, in Australia, more than 20% of women who give birth are 35 years old or older [28]. In the present study, the number of mothers who gave birth to a child with BD at the age of over 35 was 14%, which is quite a significant difference compared to the control group – 12.7%.

According to the data gathered by American scientists [10], a dependence was found for mothers aged <20 years old with the development of gastroschisis in infants (OR, 6.1; 95% CI, 4.8-8.0). However, for the age group ≥ 40 years, associations were observed in newborns with craniosynostosis (OR, 1.6; 95% CI, 1.1-2.4), hypospadias (OR, 2.0; 95% CI, 1.4- 3.0), heart defects and esophageal atresia (OR, 2.9; 95% CI, 1.7-4.9).

A group of Ethiopian doctors studied 12,225 pregnant women who gave birth to 383 (3.13%) children with BDs. According to their data, the mother's age of under 20 years ($p<0.0001$) and over 35 ($p<0.0001$) was more likely to be associated with an increased risk of children with BDs [29]. In contrast to this study, our study identified no significant difference in the diagnosis of BD in the children in the group of mothers under 20 years of age and mothers over 35.

A recent study in China is of particular interest. In 2013, the country introduced a partial two-child policy, and two years later, a general two-child policy replaced the former one-child policy approved by the government. This study observed a significant increase in maternal age and the prevalence of BDs following the new two-child policy in China [12]. In the Basque Country (Spain), the rates of chromosomal abnormalities are higher than the overall estimated prevalence in European countries and continue to increase slightly, which may be related to older maternal age [11].

However, the results of a retrospective study conducted in Latvia showed a decrease in the prevalence of BDs among newborns despite an increase in the average age of mothers in this country from 27.3 years in 2000 to 29.0 years in 2010 [30].

In our study, the age of mothers who gave birth to a child with BD was 27.3 years old and did not statistically differ significantly from the age of control group mothers. Mothers aged 20-29 years constituted 53.5% of respondents. This data matched the results of a study conducted by Indian scientists, who noted that most women (55.7%) who gave birth to a child with BD belonged to the 21–30 age group [31].

Our data are consistent with those of Korean physicians, who found no evidence that women of advanced maternal age have increased adverse maternal and perinatal outcomes compared to women aged <35, except for the high prevalence of cesarean delivery [32].

Incompatibility between a mother and a fetus can cause complications that require detection at an early stage to start appropriate treatment, in particular, hemolytic disease of the newborn, which affects children worldwide [33]. In our study, Rh incompatibility between mother and child was not significantly different between the two groups.

Folic acid supplements reduce the risk of neural tube defects in the offspring. However, their effect on other BDs remains uncertain [19]. Doctors from one of the provinces in China conducted a case-control study that included 8,379 children with congenital heart defects and 6,918 healthy children. Clinicians recommend that women of childbearing age start taking folic acid supplements as early as possible, ensuring coverage of the critical window for fetal heart development to prevent heart defects. In contrast to these data, in our study, mothers of children with BDs took folic acid half as often as mothers of healthy children.

The safety of medication use during pregnancy is of interest to clinicians, pregnant women, and society as a whole [34]. A study conducted in China [35] found that approximately one in ten pregnant women used at least one drug during pregnancy, and a significant number of them used multiple medications. This research confirmed our data, where mothers of children with BDs used medicines in the preconception period in 9.3% of cases and in the first trimester of pregnancy in 10.3% of cases.

Due to the widespread use of aspirin in obstetrics and reproductive medicine, previous studies raised concerns about potentially associated BDs. At the same time, Chinese researchers found that exposure to low doses of aspirin during pregnancy did not increase the risk of BD in the fetus, and its use during pregnancy is safe [36].

Australia has a free telephone advice service, MotherSafe, that helps Australian consumers and healthcare providers concerned about the effects of medicines during pregnancy and breastfeeding [37]. During the research conducted in 2000–2020, the service received 25,890 calls related to the exposure to anti-infective drugs during pregnancy (antibiotics, antivirals, and antifungals). Calls from patients mainly concerned the effects of drugs with a low level of risk to the fetus, while calls from healthcare professionals were about drugs with limited available information on the effects on the fetus.

Therefore, in-depth research on the potential causes of BDs, especially environmental risk factors that may require intervention, is a key component of prenatal education and primary prevention.

In our study, when comparing the anthropometric indicators of children with BDs and the control group, no significant difference was found in terms of body weight, height, head circumference, and chest circumference ($p>0.05$).

The age of mothers with children affected by BDs was 27.3 ± 6.1 years and had no statistically significant difference from the age of mothers of children in the control group - 25.6 ± 7.2 years ($p>0.05$).

There was no significant difference ($p>0.05$) in Rh conflict between a mother and fetus [OR=1.24; 95%CI: 0.76; 2.04] in both groups – 36 (2.8%) cases in the BD group and 29 (2.3%) in the control group.

Mothers who gave birth to children with BDs used drugs in the preconception period [OR=2.46; 95% CI: 1.75; 3.44] and the first trimester of pregnancy [OR=4.76; 95% CI: 3.18; 7.14] significantly more often ($p<0.05$) compared to mothers in the control group.

Pre-pregnancy preparations (tests for TORCH infections, thyroid hormones, prolactin, folic acid, and vitamins) were adequately conducted for 278 (21.6%) women who gave birth to children with BDs, which was statistically different from 563 (44%) women in the control group ($p<0.05$). [OR=2.85; 95% CI: 2.39; 3.39].

More efforts are necessary to identify drug safety issues during pregnancy and to improve the current information system for clinical practice.

Our study provides an overview of the epidemiological situation related to various factors that influence the occurrence of developmental defects. This knowledge is necessary to determine the presence of specific situations and to compare the characteristics and possible causative factors with other populations, which can lead to the identification of strategies to minimize damage.

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