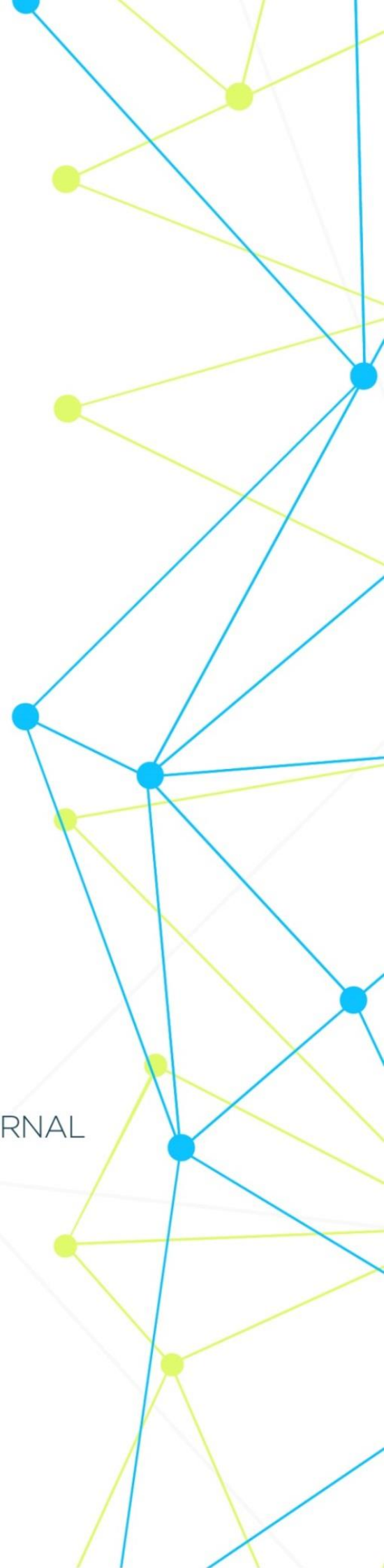


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PREVALENCE OF LADD SYNDROME IN CHILDREN IN THE STRUCTURE OF CONGENITAL DEVELOPMENTAL DEFECTS

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Background: This study examined the prevalence of Ladd syndrome and the relationship between SL and demographic factors in the Republic of Uzbekistan.

Methods: Data were obtained from the medical records of children born with congenital malformations for 5 years (2015–2020) in 13 subjects of the Republic of Uzbekistan.

Results: The total number of births was 3,759,310. 3037 cases of congenital malformations were registered, of which malformations of the digestive tract were 1315 children, among which 50 (3.8%) children were diagnosed with SL. In terms of relative risk (RR), the risk of having LS was high in newborns (RR = 1.94; 95% CI 1.47–2.56). The maximum relative risk was observed in newborns with low birth weight (RR=1.25; 95% CI 0.96 - 1.64).

Conclusion: This study analyzed the prevalence of SL in various regions of the Republic of Uzbekistan. The prevalence of LS remained stable during the study period, and the relative risk of LS was related to maternal age, birth weight, and severity.

Keywords: Ladd's band, congenital malformations, children

The urgency of the problem: According to the literature, the incidence rate of incomplete intestinal circulation in infants is 1:500 - 1:6000. It is 2 times more common in boys and girls [6, 23]. Authors of our country and the CIS countries combined numerous intestinal fixation and rotation anomalies with the concept of "incomplete intestinal circulation" [6, 8], while foreign literature uses the term "malrotation" [1, 15, 18]. Intestinal malrotation may account for up to 50% of all gastrointestinal tract infections in the infant population. In 35-40% of cases, babies are diagnosed in the 1st week of life, in 50-60% in the neonatal period [1, 3,23,31]. Congenital twisting of the midgut accompanied by hyperfixation of the duodenum is often observed, and this condition is called "Ledd's syndrome" (LS) and requires

urgent diagnosis and surgical treatment [16]. The main clinical presentation of LS is associated with intestinal obstruction caused by compression of the duodenum and twisting of the midgut, often leading to severe complications. The development of peritonitis due to circulatory failure due to torsion of the large part of the intestine or acute necrosis of the intestine can occur during intrauterine development, as well as after the birth of the baby, and can be prone to recurrence. LS are the most common form of upper intestinal obstruction (11.3%) and intestinal malrotation (37.7%) in infants [14, 23], is manifested by the development of symptoms of intestinal obstruction and peritonitis [17, 27], at the same time, it is characterized by concomitant somatic pathologies and negative prenatal factors. Usually, intestinal torsion develops in the 3-5th day of the baby, but it is noted that it develops later, even in adults [21, 23]. It is considered urgent to conduct epidemiological studies of congenital developmental defects, especially intestinal malrotation and Ladd's syndrome, to study the prevalence and incidence of these defects according to regional and demographic characteristics (gender of babies, age of mother, and region of residence). This is important not only in determining the causes and risk factors of the development of these defects, but also in creating a sufficient infrastructure and material base. Significant positive results are being achieved in infant surgery due to many studies conducted in the field of neonatology, as well as improvement of diagnostic equipment, and advances in infant intensive care. However, in developing countries, problems regarding neonatal surgical care and treatment of congenital malformations of the digestive tract remain. In addition, there is not enough scientific information on this problem from these countries [3, 13], and there are almost no scientific publications on this problem from Central Asian countries. The cited scientific aspects determine the need to study the distribution index of the defect in the region, its dynamics, in order to choose the scope of medical services and preventive measures for babies born with esophageal atresia.

The purpose of the study: To study the incidence of Ladd's syndrome among children born with congenital developmental defects in the regions of the Republic of Uzbekistan in 2015-2020 years.

Research materials and methods: The statistical indicators were analyzed of infants admitted with congenital developmental defects (CDD) to the Regional Neonatal Surgery Department of the Andijan Regional Children's Multidisciplinary Medical Center (ARCMC) as a regional institution and the Regional Neonatal Surgery Training Center (RNSTC) under the Republican Perinatal Center (RPC) as a republic institution, and the proportion of babies born with intestinal obstruction was determined. In turn, statistical data on the distribution of upper intestinal obstructions with different genesis (duodenal atresia, membrane, embryonic hernia, common pancreas) and the incidence of Ladd's syndrome in this group were studied (Fig. 1).

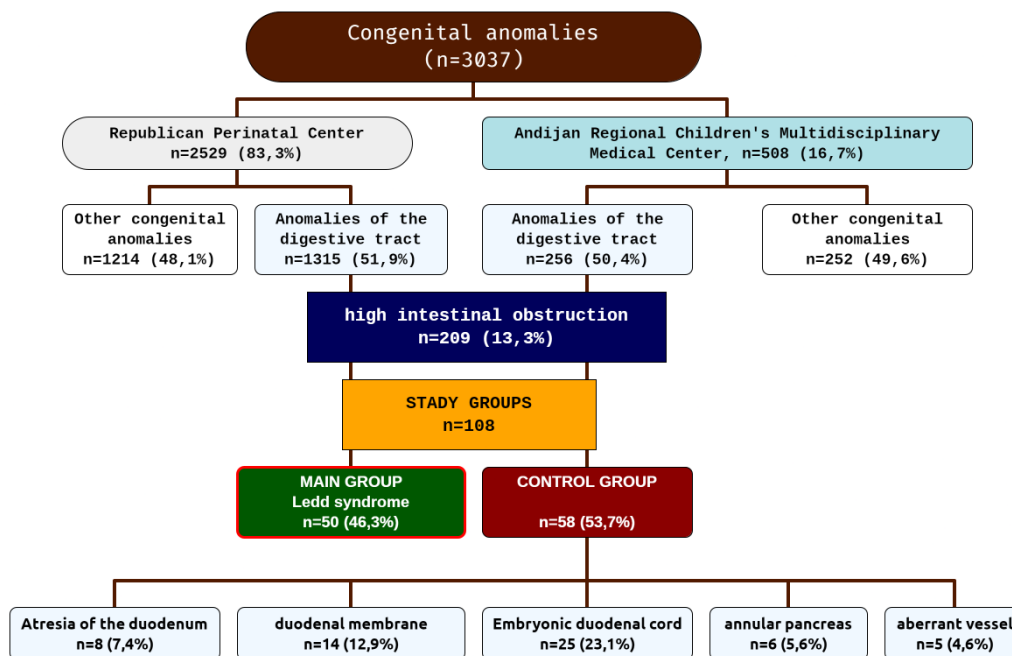


Figure 1. Research design

The research period was 5 years (2015-2020), and all the data were collected from children born in 12 regions of the Republic of Uzbekistan - Tashkent, Andijan, Fergana, Namangan, Surkhandarya, Kashkadarya, Syrdarya, Navoi, Khorezm, Samarkand, Bukhara, Jizzakh, and the Republic of Karakalpakstan received through epidemiological monitoring.

The 10th revision of the International Classification of Diseases (ICD-10) was used to record the occurrences of the defect. Children born with other congenital anomalies of the intestine (Q43.0) and congenital anomalies of rotation and fixation of the intestine (Q43.3) were included in the study. The main indicators for the analysis were the child's gender, birthweight, mother's age and the number of births. The coefficient of calculations was made in relation to the total number of live births (per 10,000 births) according to the data obtained from the statistical reports of the State Statistics Committee of the Republic of Uzbekistan. The distribution, namely prevalence (PR) of LS was calculated according to Poisson's law, with a 95% confidence interval (CI) using the Clopper-Pearson binomial "exact" method based on the β -distribution by dividing by the total birth rate. The relative risk (RR) index was used to estimate the effect of a particular factor. The significance of differences was calculated by χ^2 criteria. Dispersion statistical analysis was performed to compare the average indicators of the prevalence of the defect in different regions of the Republic of Uzbekistan. A significance level of 5% was chosen as the threshold value for all criteria.

Results: During the study period, the total birth rate in the studied regions in 2015-2020 was 3,759,310. Among them, a total of 3,037 babies were born with congenital developmental defects, 209 (13.3%) of them had upper tract birth defects with intestinal obstruction were detected. According to the analysis of appeals during the study period, in both medical institutions, the majority of patients admitted with congenital malformations were digestive tract malformations (Table 1).

	RPC	RNSTC	ARCMC		overall	
	abc.	%	abc.	%	abc.	%
Other digestive tract CDD	1164	38,3	198	6,52	1362	44,8
Upper digestive tract	120	3,95	39	1,28	159	5,23
Ladd's syndrome	31	1,02	19	0,63	50	1,64
Other organs CDD	1214	40,0	252	8,27	1466	48,3
All	2529	83,3	508	16,7	3037	100

Table 1. The number of hospitalized patients with congenital developmental defects in the cross section of institutions (abs., %)

Other congenital defects in the digestive tract, such as esophageal atresia, pylorostenosis, anorectal malformations, colon pathologies, and lower intestinal obstructions, made up 44.8% of the total number of congenital defects. In 1466 (48.3%) patients, urogenital birth defects, teratoid tumors, as well as birth defects related to the anterior abdominal wall and diaphragm defects were identified. Complete intestinal obstruction, dangerous obstruction in the form of atresia, intestinal stenosis or acute mesenteric blood circulation disorders of bowel movement was observed in 106 (50.7%) infants and toddlers and was characterized by an acute course of the disease. Intestinal permeability and partial violation of mesenteric blood circulation were observed in 95 (45.4%) patients, regardless of age and anatomical level, and the disease was chronic in these children. Also chronic-recurrent form of the disease was observed in 8 (3.8%) children with partial intestinal obstruction.

Ladd's syndrome accounted for 50 (46.3%) of birth defects with upper intestinal obstruction. This birth defect was found in 26.8% of cases in boys, in 19.5% in girls in a ratio of 1.3:1.0. According to the age period, children under 0-1 months have a higher prevalence with 21.3% and 16.7%, respectively (Fig. 2).

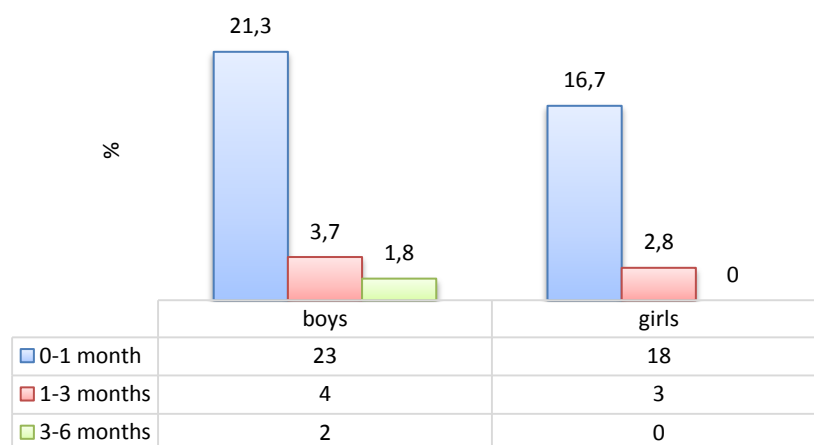


Figure 2. Distribution of children with Ladd syndrome in congenital malformations of the digestive tract by age and sex

Ladd syndrome as the only congenital defect was found in 31 (62.0%) children. 11 (58.2%) of the remaining 19 (38.0%) patients had birth defects in other organs and systems, including the cardiovascular system - 3 (27.3%), the central nervous system - 1 (9.01%), in the urogenital system - 2 (18.2%), locomotor system - 1 (9.01%), broncho-pulmonary dysplasia - 1 (9.01%). Defects in such cooperation are included in the category of developmental disabilities. 3 (27.3%) children had two or more abnormalities of the digestive tract. Overall prevalence of Ladd syndrome according to the results of the analysis was 0.11 (95% CI: 0.0911 – 1.000) per 10,000 births (Table 2).

The lowest prevalence was found in Khorezm, Surkhandarya, Navoi, Kashkadarya provinces (0.02; 95% CI 0.003-0.105), as well as in the Republic of Karakalpakstan, and this indicator was 0.08 per 10,000 births; 95%CI was 0.011-0.134, the highest prevalence of Ladd's syndrome corresponded to Tashkent region and was 0.33:10000 (95%CI 0.285-0.567), such an indicator was Andijan (0.27; 95%CI 0.135 - 0.385) and Namangan regions (0.20; 95%CI 0.076-0.297) were also observed ($p < 0.05$). It should be noted that there was no significant difference between the average prevalence of birth defects in all regions ($p > 0.05$). Also, there was no statistical relationship between the prevalence of Ladd syndrome and the geographical location of the region, but a difference in the prevalence rate was found between distant and neighboring regions ($p < 0.05$).

Regions	Overall birth incidence	cases	Prevalence (10000 per live births)	Confidence interval (95%CI)
Republic of Karakalpakstan	239 057	2	0,08	0,011-0,134
Andijon	437 129	12	0,27	0,135-0,385
Bukhara	237 911	0	0	0
Jizzakh	202 813	0	0	0
Kashkadarya	491 891	1	0,02	0,003-0,105
Navoi	129 912	1	0,08	0,003-0,105
Namangan	398 564	8	0,20	0,076-0,297
Samarkand	567 879	0	0	0
Surkhandarya	407 567	1	0,02	0,003-0,105
Sirdarya	113 258	3	0,26	0,016-0,175
Tashkent	640081	21	0,33	0,285-0,567
Ferghana	495 531	0	0	0
Khorezm	239 534	1	0,04	0,003-0,105
overall	4 601 127	50	0,11	0,911-1,000

Table 2. Average indicators and 95% confidence intervals of the Ladd syndrome occurrence rate by regions of the Republic of Uzbekistan (2015-2020, prevalence)

According to the results of the analysis of the prevalence of Ladd's syndrome in the structure of birth defects of the digestive tract recorded in all institutions of the republic, this indicator had a statistical difference in different years (Fig. 3).

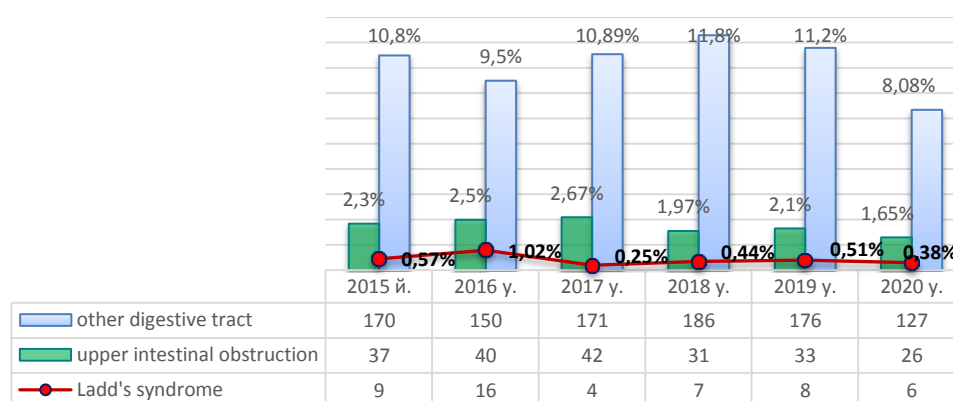


Figure 3. Dynamics of hospitalization of children diagnosed with upper intestinal obstruction as part of congenital developmental defects of the digestive tract

According to the data of the diagram, during the research period, dynamics of

birth defects of digestive tract changed over the years, and it is accounted that majority cases were in 2018-2019 years, the number of hospitalized children were equal to 186 (11.8%) and 176 (11.2%), respectively. The dynamics of hospitalization of patients with upper intestinal obstruction increased in 2015-2017, and in turn, the incidence of Ladd's syndrome increased in these years, and in 2016, with the highest rate (16, 32%), there were a total of 29 cases. As shown in Table 3 and Figure 4, the prevalence of Ladd syndrome ranged from 0.06 (95%CI: 0.026–0.201) to 0.22 (95%CI: 0.199–0.468) across the years.

years	Overall birth rates	incidences	Prevalence (per 10000 live births)	Confidence interval (95%CI)
2015 y.	734141	9	0,12	0,09-0,319
2016 y.	726170	16	0,22	0,199-0,468
2017 y.	715519	4	0,06	0,026-0,201
2018 y.	768520	7	0,09	0,069-0,262
2019 y.	814960	8	0,10	0,083-0,285
2020 y.	841817	6	0,07	0,056-0,238
Overall	3759310	50	0,13	0,911-1,000

Table 3. The prevalence rate of esophageal atresia in the Republic of Uzbekistan by year(2015-2019, prevalence)

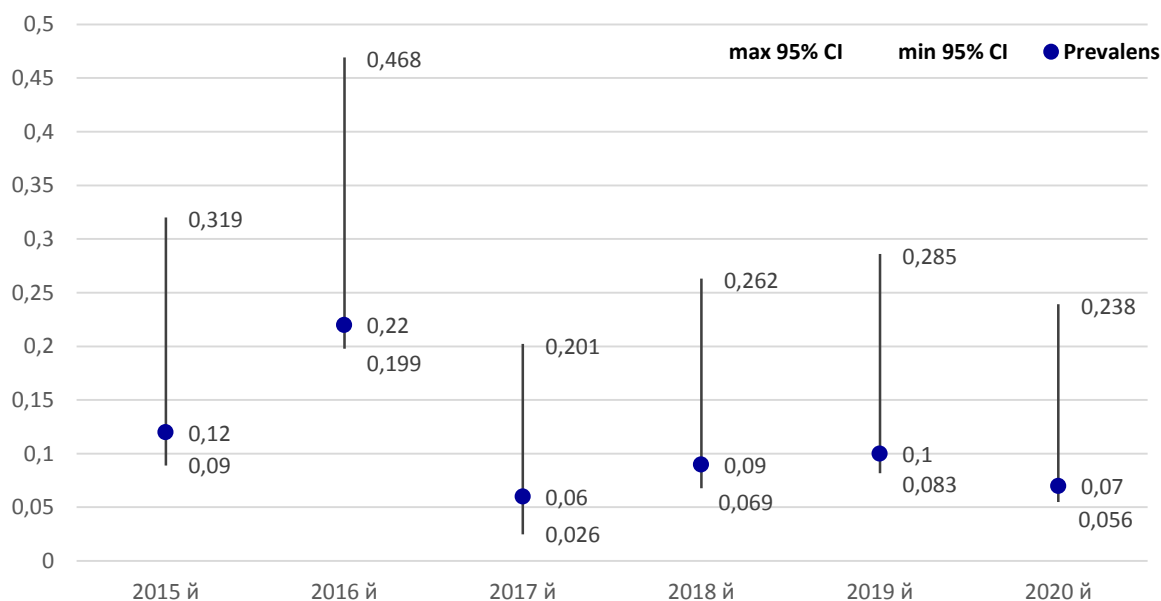


Figure 4. Average indicators and 95% confidence intervals (CI) of Ladd syndrome occurrence rates by regions of the Republic of Uzbekistan (incidence of γ -axis defect per 10,000 births)

Based on the results obtained from both medical institutions, we calculated the relative risk (RR) of Ladd's syndrome, depending on the child's gender, body weight, mother's age and pregnancy (Table 4).

Demographic factors		n	Overall birth rates	r	p	RR	95% CI
gender	Male	29	1778651	0,16	>0,05	1,54	0,877-2,696
	Female	21	1980655	0,11			
Birth weight (g)	500-2999	37	2276961	0,16	<0,05	1,85	0,985-3,486
	≥3000	13	1482345	0,09			
Mothers age	≤19	13	812458	0,16	>0,05	1,29	0,670-2,498
	20-34	28	2264104	0,12			
	≥35	9	682744	0,13			
Pregnancy	1	34	2018764	0,17	<0,05	1,83	1,011-3,319
	>1	16	1740542	0,09			

Table 4. General indicators of incidence rate (per 10,000 births) and relative risk (RR) of esophageal atresia according to various factors * - compared to 19-year-old mothers; r – share; CI - confidence interval; RR - relative risk

As can be seen from the table, maternal age 19 and younger had no effect on the risk of birth with intestinal malrotation and Ladd syndrome at the 5% level (RR=1.29; CI 0.670–2.498; $r>0.05$). However, for the first pregnancy (RR=1.83; 95% CI 1.011–3.319) as well as for low birth weight infants (RR=1.85; 95% CI 0.985–3.486) were observed to be statistically significantly higher. The maximum indicator of relative risk corresponded to children born with a birth weight of less than 3000 grams, and RR=1.85, respectively; 95% CI 0.985–3.486 and RR 1.83; 95% CI was 1.011–3.319.

Discussion: It is known that the study of the epidemiological description of diseases is necessary to determine the nature of their development, risk factors, and to distinguish high-risk groups. Congenital anomalies are one of the main causes of infant mortality, childhood morbidity and disability, and are considered one of the serious problems of the health care system [10].

According to the experts of the obstetrics, perinatal and pediatric epidemiology research group of the Center for Biostatistics and Epidemiology of the Maternité Port Royal (INSERM U1153) [3], the population level of birth defects based on a set of data obtained from regional and national programs makes it possible to estimate their

high or low rates as a reference. According to the results of this multicenter study, there was a negative correlation between perinatal death and termination of pregnancy due to congenital anomalies, and it was 75.5%. In this study, based on the data obtained from the reports of children's medical centers of the Republic of Uzbekistan, the interrelationship of digestive tract congenital defects, in particular Ladd's syndrome, with certain demographic and clinical factors was studied. A search of 30 years of scientific publications between 1992 and 2022 using the keywords "Ladd syndrome", "intestinal malrotation", "epidemiology", "prevalence" through the PubMed bio-medical research search engine included malrotation and Ladd syndrome population data. No detailed epidemiological studies were found. Most of the newly published scientific information is devoted to the epidemiology of all congenital malformations [3,5, 8,9, 13, 0] or anomalies of the digestive tract, the occurrence of malrotation syndrome [208, 12, 20], its co-occurrence with other congenital malformations [7], and the diagnosis [22, 24, 29, 30, 32] and surgical treatment [6, 19, 28]. There have also been studies investigating the incidence of intestinal malrotation in older patients [25, 26]. In particular, A. Perez and P. Pickhardt [26] studied the cases of intestinal malrotation in 11,176 adult patients according to demographic, clinical, visualization methods and surgical data based on the results of computed tomography colonography (CTC) within one center.

According to the results of the study, malrotation was detected in 27 cases (mean age 62 ± 9 years; male to female ratio 15:12), 17 of them from the CT colonography screening cohort (0.17% prevalence), 10 (75% prevalence; $p < 0.001$) detected at colonoscopy. According to these authors, CT colonography compared to optical colonoscopy, intestinal malrotation is detected 4 times more often, and this is justified by anatomical problems in endoscopy.

Some detailed information on the results of an epidemiological study on intestinal malrotation in children Published by M.B. Forrester and R.D. Merz [11]. This study examined the epidemiology of intestinal malrotation in a Hawaiian pediatric population between 1986 and 1999, based on data from the Population Registry of Birth Defects. According to the results of the study, intestinal malrotation was detected in 81 cases and was 2.86 per 10,000 live births, and the rate of malrotation was significantly higher in 1993-99 than in 1986-92 (RR=1.42; 95% CI: 1.04-1.90). According to the results of our research, the incidence rate of Ladd syndrome increased in 2015-2017 and reached a total of 29 cases with the highest rate in 2016 (16 cases, 32%), the prevalence rate over the years was 0.06 (95% CI: 0.026–0.201) to 0.22 (95% CI: 0.199–0.468) were found (Table 3, Figure 4). The reason for such differences may be the ethnic composition of the population. For example, Asians (RR=1.95; 95% CI: 1.12-3.17), Pacific Islanders (RR=2.41; 95% CI: 1.63-3.44) and significantly more frequent in Filipinos (RR=1.82; 95% CI: 1.02-

3.01). In addition, differences between populations are related to differences in data collection methods (differences in diagnosis, different variants of defects and their sampling). Taking into account such differences, it is desirable to develop national programs and registries that allow the assessment and monitoring of the level of disability for each population. According to the results of the monitoring of birth defects allow to us to control intestinal malrotations in different regions of the Republic of Uzbekistan.

It made it possible to assess the incidence of Ladd syndrome. One of the main limiting factors in our study is the relatively small number of identified cases. This is most likely due to insufficient recording or insufficient diagnosis of these defects in the institutions' registers and reports. Relatively low detection limits the power of the study, but some statistically insignificant data may be significant for a meta-analysis or a large cohort. Based on the collection of data from all regions of the republic, it became possible to study the clinical and epidemiological description of congenital developmental defects in large database. As a result of the study, in addition to the population description of this syndrome, the epidemiological description of the defect was also studied and compared with foreign research data. Also, for the first time, we estimated the relative risk of Ladd syndrome according to demographic indicators, which was recorded on the basis of the monitoring of congenital malformations. According to the results of our study, 50 (46.3%) of Ladd's syndromes were congenital defects with upper intestinal obstruction. This birth defect was found in 26.8% of cases in boys, in 19.5% in girls in a ratio of 1.3:1.0, according to the age period, children under 0-1 months were higher with 21.3% and 16.7%, respectively.

Another important risk factor for malformation is the age of the mother. One of the reasons for paying special attention to this factor in recent years is the high incidence of women giving birth at an older age in developed countries [1]. According to the results of our study, there was no effect on the risk of birth with intestinal malrotation and Ladd syndrome at the 5% level when the mother was 19 years old or younger (RR=1.29; CI 0.670–2.498; $r>0.05$). But first for pregnancies (RR=1.83; 95% CI 1.011–3.319) as well as for low birth weight infants (RR=1.85; 95% CI 0.985–3.486) this indicator was observed to be statistically significantly higher. According to the data provided by M.B. Forrester and R.D. Merz [11], the incidence rate of malrotation was inversely proportional to the age of the mother ($p=0.028$). There was no significant difference in terms of children's gender and associated birth defects, respectively, the relative risk was RR=0.98; 1.86, the 95% confidence interval was 95%CI: 0.70-1.34 and 0.38-5.44. However, the relative risk was slightly higher (RR=3.90; 95%CI: 2.83-5.24) in infants with a birth weight of less than 3000 grams. Such changes were observed in our study.

Thus, during this study, the distribution and meeting characteristics of Ladd's

syndrome were determined depending on the studied indicators, and these characteristics almost coincided with the data of other scientific publications. At the same time, the continuous study of the epidemiology of Ladd's syndrome within the framework of the monitoring of congenital developmental defects serves as a basis for determining not only this defect, but also the clinical demographic factors of anomalies with intestinal rotation disorders in the composition of congenital defects, and in turn, the mortality rate, morbidity and serves to a certain extent to determine disability.

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