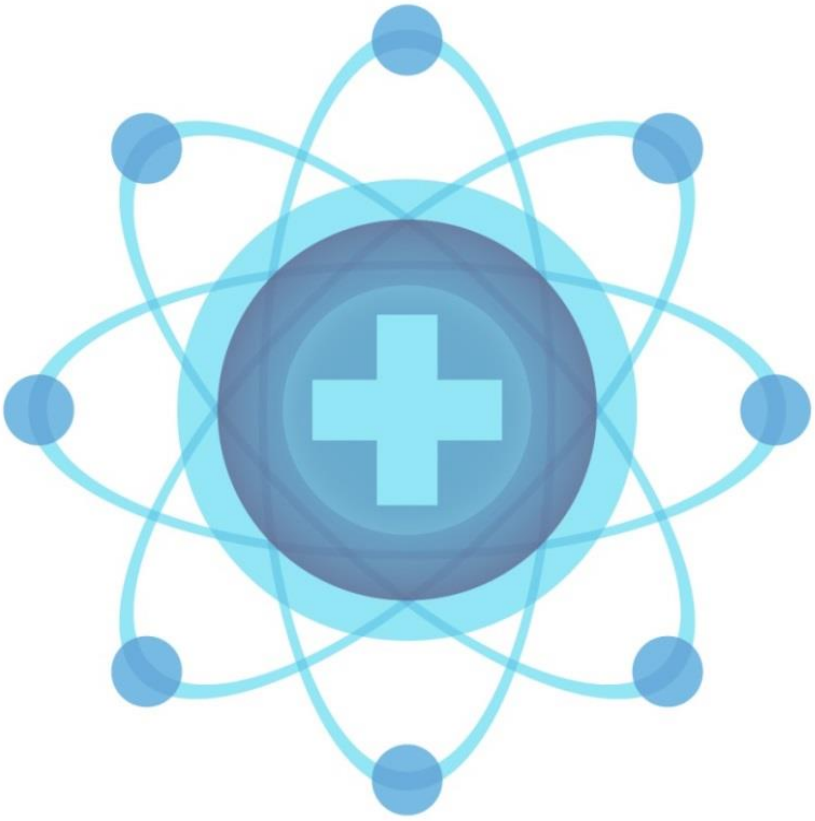

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DESCRIPTIVE EPIDEMIOLOGY OF ESOPHAGEAL ATRESIA IN NEWBORN

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Abstract: The article presents the results of an epidemiological study of esophageal atresia in the structure of congenital malformations. These results are based on a five-year monitoring of congenital malformations in 13 regions of the Republic of Uzbekistan for the period 2015-2020.

During the study period, the overall frequency of AP with interregional difference was 0.62 per 10000 (95% CI 0.49-0.64) or 1 in 16129 newborns and remained stable over time. Fistulous forms occurred in 96.6%, non-fistulous forms in 3.4% of children. Among newborns with AP, congenital heart defects were observed in 58%, gastrointestinal tract in 25.9%, urinary system in 17.3%, musculoskeletal system in 7.7% of patients. CNS defects and other disorders occurred in 4.81% of cases. In terms of relative risk (RR), the risk of having AP 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).

Keywords: congenital malformations, esophageal atresia, epidemiology, frequency, newborns

Actuality: The trachea and esophagus are formed by the division of a single tube consisting of the foregut endoderm [03, 4, 5, 6]. Despite the different scientific views on this matter, the authors agree that it consists of a fundamental morphogenetic process, such as the separation of the respiratory and digestive tubes from the proximal part of the foregut [7]. This process depends on the temporal and spatial patterns of expression of a number of genes that form the foregut [8]. Their disruption causes disruption of the anterior intestinal compartment, and, in turn, tracheo-esophageal malformations [9, 10, 11, 12, 13, 14]. Disruption of these

processes leads to the development of congenital defects such as esophageal atresia [15, 16, 17, 18] and tracheo-esophageal fistula [19, 20]. These defects cause swallowing and breathing difficulties of the baby, requiring timely diagnosis [21] and surgical procedure [22].

According to the information of a large number of CIS countries and foreign authors on the treatment of esophageal atresia in infants, despite a number of achievements, many problems in this regard, as well as problems related to technical aspects, have not been solved [23, 24], and the mortality rate due to this pathology ranges between 40-60% [24, 26]. Especially in babies with concomitant somatic diseases, there are difficulties in eliminating this defect [27, 28]. The largest contribution of accompanying somatic diseases corresponds to aspiration pneumonias [29, 30, 31, 31]. In addition, in fistula forms of esophageal atresia, 50% of cases are accompanied by additional anatomical anomalies [33, 34]. Cardiovascular [35, 36, 37], urinary-genital [38], digestive system [39, 40], locomotor system [41, 42], as well as central nervous system [43] defects are 35%, 24%, 24%, 13% and 10% of cases respectively occurs [44, 45]. In 36% of cases, the fistula type of esophageal atersia appears as a component of VACTERL-syndrome [46, 47, 48, 49, 50, 51].

Significant positive results are being achieved in infant surgery due to many researches conducted in the field of neonatology, as well as improvement of diagnostic equipment, and advances in infant intensive care. However, in developing countries, neonatal surgical care and treatment of esophageal atresia remain problematic, especially in emergency settings [52]. In addition, there is little scientific information on this problem from these countries, and there are almost no scientific publications on esophageal atresia from Central Asian countries [53]. In developing countries, the mortality rate from esophageal atresia still ranges from 30% to 80%, and this indicator requires a radical improvement of medical care measures for this category of patients [54, 55]. In the publications of these countries, the authors note that there are problems in diagnosis and/or referral in infants with esophageal atresia [56, 57] . It is considered urgent to conduct epidemiological studies of congenital developmental defects, in particular, esophageal atresia, to study the prevalence and level of occurrence of these defects according to regional and demographic characteristics (gender of babies, age of mother, 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.

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 prevalence of esophageal atresia among children born with congenital developmental defects in the regions of the Republic of Uzbekistan in 2015-2019.

Research material and methods of investigation. In order to study the incidence of esophageal atresia in infants, archival materials of 3037 infants born with congenital developmental defects were sent to the Department of Neonatal

Surgery of the Ministry of Health of the Republic of Uzbekistan, the Neonatal Surgical Training-Treatment-Methodological Center of the Republic Perinatal Center and the Regional Neonatal Surgery Department of the Andijan Regional Multidisciplinary Medical Center (AVBKTTM) during 2015-2019 years were analyzed. These materials also included information on live births and stillbirths at perinatal centers and children's medical centers. According to the clinical reports of these centers, a total of 3,037 babies with congenital developmental defects were hospitalized in 2015-2019 (Table 1).

Type of birth defects	**Institutions**				**Everything**	
	RPC NHODUM		AVBKTTM			
	abs.	%	abs.	%	abs.	%
Esophageal atresia	196	7.8	38	7.4	234	7.7
Other congenital malformations of the digestive tract	1119	44.2	218	42.9	1337	44.0
Other organs congenital malformations	1214	48.0	252	49.6	1466	48.3
Total	2529	100	508	100	3037	100

Table 1. With congenital developmental defects in the cross-section of institutions
Number of hospitalized babies (abs., %)

Among them, the number of babies hospitalized with congenital malformations of the digestive tract was 1337 (44.0%). 234 (17.5%) of congenital malformations of the digestive tract corresponded to esophageal atresia (Fig. 1).

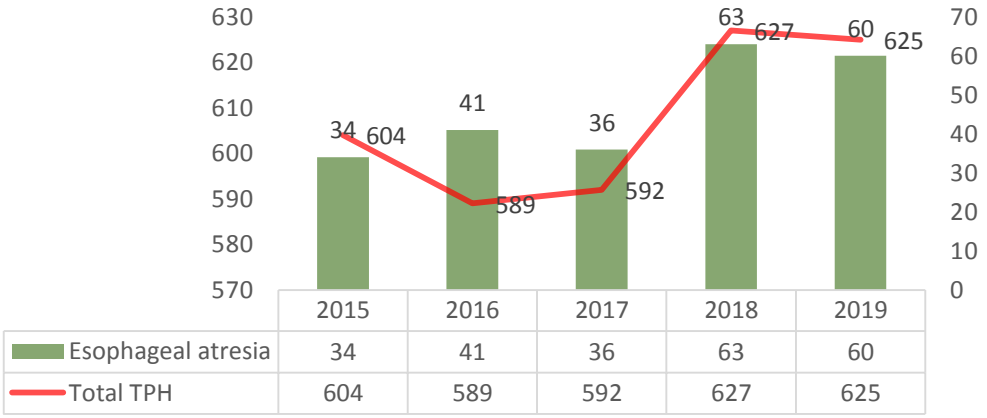

Figure 1. Dynamics of hospitalization of infants diagnosed with congenital malformations and esophageal atresia

Premature babies made up 28% of the group of babies born with congenital defects of the digestive tract. Preterm birth is most often associated with esophageal

atresia (47%), gastroschisis (78%), and intestinal obstruction (25% to 28%), and less frequently with anorectal birth defects (8%), diaphragmatic hernia (9%), and omphalocele (7). %) was observed. In addition, 21-30% of babies born with congenital malformations have intra-fetal hypotrophy, and 4% of babies are born with multiple pregnancies. A low Apgar score (less than 7 points) was found in infants born with diaphragmatic hernia (78%), esophageal atresia (56%) and anterior abdominal wall defects (48%). According to the received data, the share of somatic diseases that could affect the results of treatment among babies with birth defects was 19%. According to the course of pregnancy, the percentage of pregnant women with a complicated obstetric anamnesis was 75%, and in 20% of cases, deliveries were performed surgically, mainly according to obstetrician's instructions. A retrospective cross-sectional cohort study was conducted in registered infants born with esophageal atresia and tracheoesophageal communication to determine the incidence of the defect. Annual reports and regulatory documents of regional children's medical institutions where babies born with birth defects are admitted for research were also studied. According to the territorial characteristics, each region covered a 5-year representative sample between 2015 and 2019, which included all types of diagnosed esophageal atresia with and without fistula. All data were selected based on characteristics such as region, infant gender, gestational age, birth weight, maternal age. The coefficient of calculations was made in relation to the total number of live births according to the data obtained from the statistical reports of the State Statistics Committee of the Republic of Uzbekistan. The incidence rate and relative risk of esophageal atresia were calculated according to infant sex, body weight, maternal age, and gestational age. The prevalence (PR) of esophageal atresia was calculated 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 according to Poisson's law. The relative risk (RR) index was used to estimate the effect of a particular factor.

Research results. A total of 234 cases of esophageal atresia with and without fistula were identified during the study period. 226 (96.6%) of them had esophageal atresia with fistula, and 8 (3.4%) had esophageal atresia without fistula. Proximal tracheo-esophageal fistula was detected in 9 (3.85%) babies from fistula types ("V" type), and 5 (2.14%) cases had 2 esophageal atresia with fistulas ("D" type). In the remaining 212 (90.6%) infants, esophageal atresia with distal esophago-tracheal fistula ("S" type) was detected. This defect was noted in 56% of cases in male babies, and in 44% of female babies, and the ratio was 1,3:1,0. 95.6% of all births were live births and 4.4% were stillbirths. Among babies born with congenital defects of the digestive tract, the incidence of premature babies was 28%. According to the results of the analysis, the prevalence of esophageal atresia was 0.62 (95% CI: 0.49-0.64) per 10,000 births.

According to the data of the State Statistics Committee, the total number of births in 12 regions of the republic and the Republic of Karakalpakstan from 2015 to 2019 was 3,759,310 (Table 2).

Areas	Birth rate	The number of encounters	Prevalence (per 10000)	Confidence Interval (95%CI)
KarkalpakistanResp.	199771	7	0.35 _ _	0 , 11-0 , 59
Andijan region	355704	38	1 , 0 6	0 , 73-1 , 4
Bukhara region	196356	4	0.2	0 , 03-0 , 37
Jizzakh region	164695	8	0.49 _	0 , 17-0 , 79
Kashkadarya region	401561	12	0.30 _	0 , 14-0 , 46
Navoi region	106024	4	0.38 _	0.05-0.07
Namangan region	323844	42	1.30 _	0 , 91-1 , 68
Samarkand region	466465	4	0 , 0 8	0 , 02-0 , 19
Surkhandarya region	332909	12	0 , 3 6	0 , 16-0 , 55
Syrdarya region	92205	12	1.30 _	0 , 59-2 , 0
Tashkent region	519726	84	1.61 _	1 , 25-1 , 94
Fergana region	402494	4	0 , 10	0 , 01-0 , 18
Khorezm region	197556	3	0 , 15	0 , 05-0 , 45
Total	**3759310**	**234**	**0.62 _**	**0 , 49-0 , 64**

Table 2. The prevalence rate of esophageal atresia in the regions of the Republic of Uzbekistan (2015-2019, prevalence)

Differences in the prevalence of birth defects were found between the regions involved in the study. The lowest prevalence was found in Fergana region and this indicator was 1.26 (95%CI, 0.01-0.18) per 10,000 births, while the highest prevalence of esophageal atresia was in Tashkent region and was 1,61 :10000 (95%CI, 1.25-1.94). The statistical significance of this difference is $p<0.05$. It should be noted that there was no significant difference ($p>0.05$) in relation to the average prevalence of birth defects in all regions. Also, there was no statistical correlation between the distribution of esophageal atresia and the geographical location of the area, but a difference in the distribution index was found between distant and neighboring areas ($p<0.05$).

According to the results of the analysis of the prevalence of birth defects recorded in all institutions of the republic, this indicator had a statistical difference in different years ($p<0.01$) and ranged from 0.44 to 0.64 per 10,000 births. However, no regularity was observed in the changes in the prevalence of esophageal atresia over the years (Table 3, Figure 2).

Years	Birth rate	The number of encounters	Prevalence (compared to 10000)	95% CI
2015 _	734141	37	0 , 44	0 , 31-0 , 62
2016 _	726170	57	0 , 70	0 , 53-0 , 92

2017 _	715519	49	0 , 64	0 , 48-0 , 86
2018 _	768520	52	0 , 59	0 , 44-0 , 78
2019 _	814960	39	0 , 44	0 , 32-0 , 61
Total	**3759310**	**234**	**0 , 56**	**0 , 49-0 , 64**

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

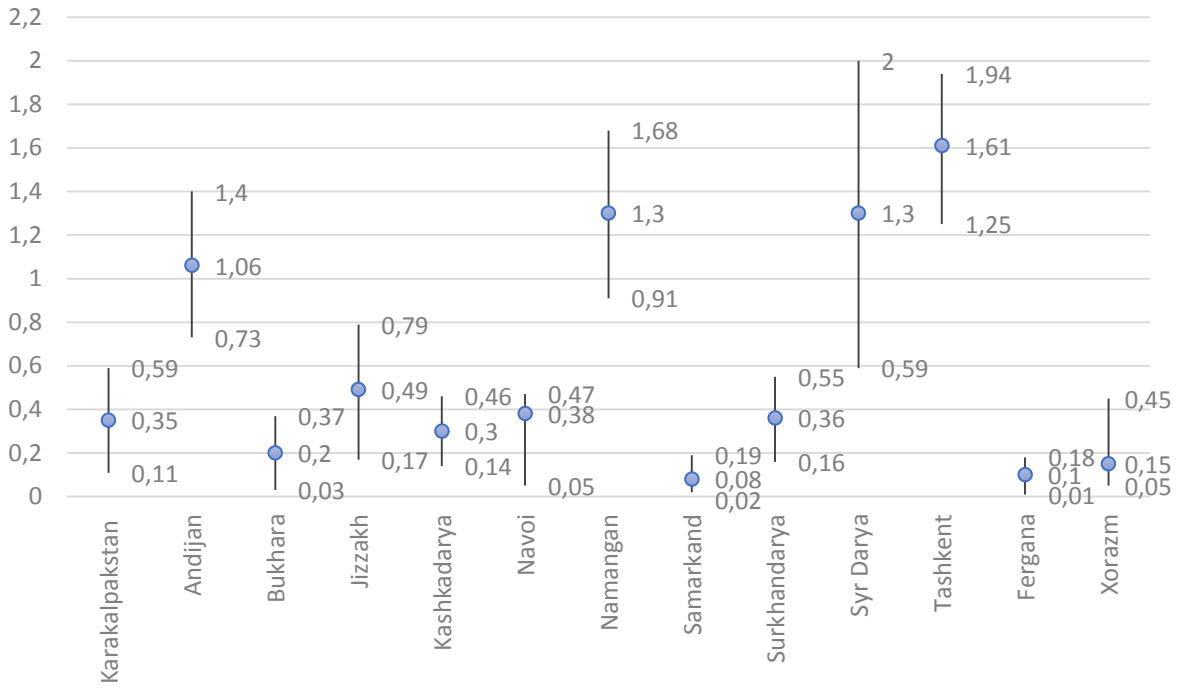

Figure 2. Average indicators and 95% confidence intervals of the incidence of esophageal atresia in the regions of the Republic of Uzbekistan (γ-axis defect per 10,000 births)

According to the diagram, the dynamics of esophageal atresia changed over the years during the study period, and the number of children with this problem was the majority in 2016-2018 and was 57, respectively (PR-0.70; 95%CI: 0.53-0.92), 49 (PR-0.64; 95%CI: 0.48-0.86) and 52 (PR-0.59; 95%CI: 0.44-0.78)186 (11.8 %) corresponded to the baby. We calculated the relative risk (RR) of esophageal atresia depending on the child's sex, body weight, mother's age and pregnancy (Table 4).

Demographic factors		n	Birth rate	r	p	RR	95% CI
Sex	Son	123	1778651	0.69	<0.05	1.23	0.95-1.59
	Girl	111	1980655	0.56			
At birth body weight (g)	500-2999	154	2276961	0.68	<0.05	1.25	0.96-1.64
	≥ 3000	80	1482345	0.54			
Mother's age	≤ 19	24	812458	0.29	<0.01	0.39	0.26-0.61

	20-34	168	2264104	0.74			
	≥ 35	42	682744	0.61	<0.001	2.08*	1.26-3.44*
Birth parity	1	162	2018764	0.80	<0.001	1.94	1.47-2.56
	>1	72	1740542	0.41			

* - in relation to 19-year-old mothers; r – portion ; CI is confidence interval ; RR – relative risk

Table 4. The incidence of esophageal atresia depends on various factors (per 10,000 births) and relative risk (RR) general indicators

As can be seen from the table, maternal age 19 and younger had no effect on the risk of giving birth with EA at the 5% level. However, the relative risk for mothers older than 35 years (RR=2.08; 95% CI 1.26–3.44) and for first pregnancy (RR=1.94; 95% CI 1.47–2.56) was also was found to be high. Also for boys (RR 1.23; 95% CI 0.95 - 1.59) and low birth weight babies (RR=1.25; 95% CI 0.96 - 1.64) , it was observed that this indicator is statistically more reliable. The maximum relative risk was for mothers aged 35 and over and number of pregnancies and RR=2.08, respectively; 95% CI 1.26–3.44 and RR 1.94; The 95% CI was 1.47–2.56.

Thus, conducting epidemiological studies on congenital malformations, especially esophageal atresia , is of great importance in studying the distribution of these malformations according to territorial and demographic characteristics (race, gender, age of the mother, etc.). Also, the assessment of the regional indicator of the occurrence of esophageal atresia , the study of its dynamics makes it possible to choose preventive measures and the amount of medical assistance.

Discussion. Studying the prevalence rate of birth defects based on data from regional registries, databases or national programs, assessing their prevalence serves to identify areas with high and low prevalence of this rate [58, 59, 60, 61]. Another advantage of these systems and registries is that they have the ability to standardize data collection and cover all regions, which allows studying the epidemiological description of birth defects, especially their rare forms. The results of our study showed that the prevalence of esophageal atresia varies even in different geographical areas of the same country .

esophageal atresia in European countries were demonstrated by the EUROCAT (European Surveillance of Congenital Anomalies) system, which includes regional registries and conducts population studies [62]. According to EUROCAT data, the prevalence of esophageal atresia with and without fistula among live and stillborn infants was 2.19 per 10,000 between 2001 and 2018. For example , the prevalence of esophageal atresia was 0.58 in one area of Ireland, while this indicator reached 3.99 in Strasbourg (France).

This indicator was also recorded differently for different states of the United States of America, for example, in Hawai it was 2.24 per 10,000 births, for the state of Texas it was 2.33:10 000 and for the state of California it was 2.82:10 000 [63].

The reason for the differences mentioned above may depend on the ethnic composition of the population. For example, the lowest prevalence of esophageal atresia has been reported in Latino American and Afro-American populations. On the other hand, the reason for such a significant difference in the prevalence of esophageal atresia among the population is considered to be different methods of data collection and approaches to it (variety of diagnosis), defects in recording birth defects, social, environmental, population factors or anthropogenic influences on the environment, or genetic predispositions are possible Therefore, the exact explanation of such significant differences in the regional distribution of EA is somewhat complicated.

Demikova N.S. and co-authors, the prevalence of esophageal atresia varied in different regions of the Russian Federation and ranged from 1.26:10,000 (95% CI, 0.68–2.35) to 2.81:10,000 (95% CI, 2, 29–3.45), with a mean prevalence of 2.03:10000 (95% CI, 1.92–2.25) across 24 regions of the RF, or 1 in 4926 births with esophageal atresia . [60] . These figures were noted to be consistent with data provided by EUROCAT and the International Center for Data Sharing on Birth Defects Surveillance and Research (ICBDSR).

Esophageal atresia has remained stable over the past 3 decades, regardless of geographic location, study period, and data collection methods. Pedersen R.N. and co-authors have shown that the prevalence rate of esophageal atresia was 2.37 and 2.46 per 10,000 births, respectively [63]. The changes between these two decades were not statistically significant. Based on the data obtained through various programs, it is emphasized that the differences in the prevalence of esophageal atresia are not the real factors affecting the development of this risk, but local factors affecting the registration of births with esophageal atresia [64].

Thus, there is sufficient data on the prevalence of esophageal atresia and the high survival rate with this defect in developed countries. However, due to the high rate of incidence of esophageal atresia in developing countries, there is no possibility to obtain real data on these indicators due to the lack of unified systems that record this defect and the incompleteness of the existing data. In addition, the researchers of these countries published few important publications [66, 67, 68]. It should be noted that in developing countries, the mortality rate of babies born with esophageal atresia ranges from 30 to 80%, which requires a radical reform of medical services for this category of patients .

In studies published by these countries, late diagnosis of the defect and/or late referral of the patient to specialized centers are indicated as the reason [69]. In addition, non-availability of permanent aspiration equipment, complications such as sepsis and aspiration pneumonia, as well as lack of specially trained medical personnel create obstacles to providing qualified medical care [70, 71].

During the study, the monitoring of congenital malformations made it possible to estimate the prevalence of esophageal atresia in the Republic, and according to its results, it was shown that the prevalence of esophageal atresia is different in different regions. The overall prevalence of esophageal atresia by region ranged from 0.08 (95% CI, 0.02–0.19) to 1.61 (95% CI, 1.25–1.94) per 10,000 live births. It was

determined that the average prevalence of esophageal atresia in 13 regions of the republic is 0.62 (95% CI 0.49-0.64) per 10,000 babies, in other words, 1 in 16,129 babies.

As a result of our study, an epidemiologic description of esophageal atresia was presented, and it was found that the incidence of esophageal atresia was significantly lower in our study compared to other studies such as EUROCAT and the International Center for the Sharing of Data on Birth Defects Surveillance and Research (ICBDSR). The reason for this is not the actual low birth rate of babies with congenital developmental defects, especially esophageal atresia, but the fact that there is no single system that records defects in the regions of our Republic that assist with childbirth and children's treatment and prevention institutions, and due to the incompleteness of the existing data, there is no possibility to obtain real data on these indicators. It should be noted that it is not always possible to fully analyze medical documents for statistical analysis (lack of complete information in the archive, loss of medical history or any examination results, sending medical documents to different organizations for expert opinions, etc.). In order to eliminate this problem, we have developed a quality register for the control of birth defects and created an electronic platform for it. This electronic platform received a patent from the intellectual property agency for the computer program "Quality register for the control of birth defects in neonatal surgery" (No. DGU 14702. State register of the Republic of Uzbekistan. Date of registration: 22.02.2022) and put it into practice.

As mentioned above, according to our data, esophageal atresia is more common in boys. Similar gender-specific results were reported in other studies, and in these studies, the fistula type of esophageal atresia was also taken into account [72].

One of the important risk factors for birth defects is the age of the mother. Due to the fact that women in developed countries are having children at a somewhat older age, the study of this factor has become particularly important in recent years. Because of this, there is a need to study the relationship between mother's age and birth defects. The results of our study showed that mothers older than 35 years of age have a high risk of having babies with esophageal atresia . A significant difference in the prevalence of malformations was found in this group compared to mothers in other age groups (RR=2.08; 95% CI 1.26–3.44). Other studies have reported that the risk increases with maternal age [73]. Also, male gender (RR 1.23; 95% CI 0.95 - 1.59) and low birth weight infants (RR=1, 25; 95% CI 0.96 - 1.64) was observed to be statistically significantly higher, albeit insignificantly. The maximum relative risk was for mothers aged 35 and over and number of pregnancies and RR=2.08, respectively; 95% CI 1.26–3.44 and RR 1.94; The 95% CI was 1.47–2.56. The results of the study showed that there is a statistical relationship between the risk of QA and the number of pregnancies, in particular, we noted a higher risk of birth with QA among first children (RR=1.94; 95% CI 1.47–2.56). The highest relative risk was observed in low birth weight infants (RR=1.25; 95% CI 0.96 - 1.64). There are research studies in which the same ratio is found in literature data [73].

In conclusion, it should be noted that esophageal atresia occurs on average in 1 in 4099 infants worldwide and remains dynamic over time. Differences between cases observed by congenital malformation surveillance programs may be due to factors influencing the recording of esophageal atresia cases.

Conclusions . This study included the first epidemiological studies on esophageal atresia in the Republic of Uzbekistan, according to its results, the overall prevalence rate of esophageal atresia was 0.62 (95% CI 0.49-0.64) per 10,000 babies with regional differences, and remained stable over time. The association between esophageal atresia and demographic factors reported in this study was not significantly different from results reported in other studies.

Introduction of a single system including monitoring programs and databases in the regions of our republic that assist childbirth and children's treatment-preventive institutions will create an opportunity to obtain real information on birth defects and improve their treatment methods.

As part of the monitoring of congenital developmental defects, it serves as a basis for determining the clinical-demographic factors of the study of the epidemiology of esophageal atresia, and in turn, contributes to determining the level of mortality, morbidity and disability among children in the country.

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