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Prevalence and Factors Associated with Congenital Malformations in Tirana, Albania, During 2011-2013

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ABSTRACT

Aim: Congenital Malformations (CMs) represent a challenge especially for developing countries. Data about CMs in Albania are rather scarce. In this context, our aim was to assess the prevalence and factors associated with CMs in Tirana, the capital of Albania. **Methods:** Information on all CMs at birth during 2011-2013 was retrieved from the National CM Surveillance System. For each CM case, three controls (babies born without CM) were retrieved as well. Overall, 831 cases and 2522 controls were included in this study. The prevalence was calculated using the total number of live births in Tirana during the same period. Binary logistic regression was used to determine the factors associated with CMs adjusting for a number of covariates. **Results:** The three-year prevalence of CMs was 23.41 per 1,000 live births. The most affected body systems were the musculoskeletal, cardiovascular and genital systems. CMs were more prevalent among male babies. Advanced mothers' age, lower education, unemployment status and lower gestational age were all positively associated with increased likelihood of CMs. **Conclusions:** Socio-demographic factors of mothers are linked to CMs in Albania. Future surveys are needed in Albania in order to establish determinants of CMs at a national level.
Keywords: Albania, congenital malformations, epidemiology, Tirana.

1. INTRODUCTION

Congenital malformations (CMs) represent a well-known public health problem and an issue of growing concern (1). According to March of Dimes (MOD), every year there are 7.9 million children born with a serious CM of genetic or partially genetic origin, accounting for 6% of all births worldwide (1). Serious congenital malformations can be lethal or cause mental, physical, auditory and/or visual impairment. Worldwide, at least 3.3 million of children less than five years of age die from CMs each year and an additional 3.2 million remain with different degrees of disabilities (1). CMs represent an especially challenging problem for the developing countries where more than 94% of serious congenital malformations and 95% of deaths from such malformations occur (1).

According to MOD, the most common serious congenital malformations were: congenital heart defects, neural tube defects, hemoglobin disorders (thalassemia and sickle cell disease), Down syndrome and glucose-6-phosphate dehydrogenase deficiency (G6PD) (1). CMs can be caused by genetic or non-genetic factors and in many cases, genes and environment contribute together to cause a congenital malformation (2). CMs can cause enormous harm where elevated risk factors are present and health care is limited (3).

Air pollution, parental agriculture work, especially maternal involvement during the acute risk period (first trimester of pregnancy) was found to be associated with a number of selected congenital malformations (4, 5, 6). Poverty might also increase the risk of CMs (1). In addition, the association between CMs and maternal age has been well studied (1, 7, 8). Recently attention has turned to paternal age as a possible predictor of congenital malformations (9, 10, 11) even though previous reports did not regard paternal age as a significant contributor in the overall prevalence of CMs (1) . Maternal smoking (12, 13) and alcohol use (14, 15, 16, 17) during pregnancy has been associated with certain CMs as well. Furthermore, ethnic differences in the prevalence of CMs have also been reported (18).

The prevalence of CMs varies in time as well as between countries and between regions within countries and there are different explanations put forward for this variability (19, 20, 21, 22). Clearly, high income countries are characterized by low prevalence of CMs compared to middle and low income countries, suggesting for possible influences of health care, environmental quality and poverty (1, 21). Consanguineous marriages, prevalent in certain parts of the world could also explain a part of the CMs prevalence variability (1).

The information about CMs and factors associated with it is very scarce in Albania, a South-Eastern European (SEE) country characterized by a long transition period and massive population displacements. According to the 2011 Census, in 1 October 2011 the total number of residents in Albania was 2,821,977 (23). The number of births has declined substantially from around 53 thousands in 2001 to around 34 thousands in 2011 (23). In Tirana region resides 26.7% of the total population (23) whereas around 32% of all live-births occur in Tirana (24), the capital city of Albania. International figures regarding CMs in Albania are mainly based on estimations (1). According to MOD's 2006 global report, Albania ranks among the countries with a moderate prevalence of CMs (52.9 per 1,000 live births) ranking in 137th place out of 192 countries included in analysis (1).

In national level, the local information about CMs in Albania still remains largely scarce. The only figures being routinely reported until recently were the total number of CMs, the number of individuals born with spina bifida and congenital dislocation of hip (24, 25). Only in 2009, through an order of the Minister of Health, data about CMs in Albania started to be collected on scientific basis (26). Following the improvement in the quality and rates of reporting, there has been some information regarding the prevalence of CMs in Albania which are much lower compared to international figures. For instance, the overall prevalence of CMs per 1,000 live births in Albania in 2010, 2011 and 2012 was 14.0 (25), 15.2 (27) and 14.3 (27), respectively. However, there is no scientific information about the factors associated with CMs in this SEE transitional country. In this context, the aim of this study is to assess the factors associated with CMs in Tirana, the capital of Albania.

2. METHODS

Study population

This is a cross-sectional survey reporting data on all CMs diagnosed at birth at the two public obstetric-gynecologic hospitals in Tirana, the capital of Albania, during 2011-2013 time period. Data on CMs are now routinely reported to the National Congenital Malformations Surveillance System (NCMSS), which has been described elsewhere (26,27). Normally, the NCMSS should retrieve data on CMs from all the regions of the country, but the system is still facing considerable challenges in terms of reporting rates, especially from private hospitals which carry out deliveries (26, 27). On the other hand, CM data about Tirana are more complete compared to data coming from other regions of the country and for this reason our survey focused on the capital city.

In order to assess the factors associated with congenital malformations in Tirana, we also retrieved information about babies born without congenital malformations in Tirana. For every CM case diagnosed at birth, three babies born without CMs were selected randomly from the list of normal babies born in the respective study years. Because of this random selection and because not every filled in the birth registries is filled in, due to several reasons, there was some missing information in 564 normal born babies regarding the education and employment status of the mother. However, because there was information regarding other important variables, we retained these cases for descriptive purposes.

Data collection

We retrieved information about the age of the mother. This variable was then recoded into a three-category ordinal variable based on tertiles (<25 years, 25-30 years, >30 years). The educational status of the mother was available only in categories (≤secondary education-≤8 years of formal schooling, high school education-9 to 12 years of formal schooling, university education). Other variables for which information was available were mother's place of residence (urban vs. rural), mother's employment status (unemployed vs. employed) and gestational age, in weeks. As regards the baby, there was information about sex (male, female, hermaphrodite) and birth weight expressed in grams.

There was detailed information about the type of CM among CM cases, based on ICD-9 codes (26,27). Based on this information it was possible to report CMs according to the affected system.

Statistical analysis

Absolute numbers and respective percentages for categorical variables and mean values and standard deviation for numerical continuous variables were reported. Chi square test and student's t test were used to detect any significant difference between categorical and numerical variables, respectively.

The overall and yearly prevalence rate of CMs in Tirana was calculated based on the respective number of live births, expressed per 1,000 live births. We also reported the proportional prevalence of CMs by type of body system affected among all CM cases (expressed in percentage) and the overall prevalence of CMs' types against all live births in Tirana (per 1,000 live births).

To assess the factors associated with CM in Tirana, we used the binary logistic regression procedure. First we reported the crude (unadjusted) odds ratios (ORs) and then, in a second model, we adjusted simultaneously for mother's age, education, employment status, place of residence, gestational age, sex of the baby and birth weight in order to control for potential confounding effects using the "enter" method. The multivariable-adjusted binary logistic regression model relied on 2774 individuals for whom there was completed information about the variable included in the study.

Associations were regarded as significant if the P-values were ≤0.05. Statistical Package for Social Sciences software (SPSS), version 17 was used for all the statistical analysis.

3. RESULTS

In total 3353 individuals were included in the study. The average age of mothers was 27.75 years (±5.17 years), significantly higher among CM babies' than non-CM babies' mothers (28.89 years vs. 27.37 years, respectively, P<0.001) (Table 1). Significantly higher proportions of CM babies' mothers had low education level compared to normal babies' mothers (48.5% vs. 24.5%, respectively, P<0.05). Significantly more mothers having CM babies were unemployed and of rural residence compared to mothers with normal babies (Table 1). About two thirds of CM babies were males (63.2%) compared to just 50% of males among controls (P<0.05). The gestational age and birth weight of CM babies were both lower compared to those of babies without CMs (Table 1).

The overall prevalence of CMs in Tirana for the period 2011-2013 was 23.41 per 1,000 live births, with little fluctuations across the study years: 24.77 per 1,000 live births in 2011, 25.83 per 1,000 live births in 2012 and 20.06 per 1,000 live births in 2013 (Table 2). The body system most commonly affected by CMs was the musculoskeletal system accounting for 23.3% of all CM cases during 2011-2013 followed by the cardiovascular system accounting for one fifth (20.2) of all CM cases detected during 2011-2013 (Table 2). Cardiovascular CMs accounted for almost one quarter of all CM cases in 2011 (24.5%) and 2012 (24.0%) but only 11% of CM cases in 2013 (Table 2). The respective figures for musculoskeletal CMs were 20.2%, 19.3% and 31.4%.

The overall prevalence of CMs per 1,000 live births by type of system affected followed closely the trends of proportional prevalence of CMs (Table 2).

Regarding the factors associated with CMs, Table 3 presents a detailed picture. In crude analysis, the likelihood of CMs was significantly higher among older, least educated, rural resident and unemployed mothers (Table 3). A significant inverse relationship was detected between the presence of CMs with gestational age and birth weight. In multivariable-adjusted models, the relationship of CMs with place of residence turned not-significant, the associations with education level and employment status became weaker whereas the associations with mother's age and baby's sex were slightly strengthened. After multivariable-adjustment analysis, mothers older than 30 years of age were 2.40 times more likely to have CM babies compared to mothers aged less than 25 years (OR=2.40, P<0.001). Having low education level, being unemployed and being a male baby were associated with 2.03, 2.37 and 1.83 folds, respectively, higher likelihood of experiencing any CM whereas increasing gestational age was a protective factor. The birth weight of the baby was not associated with the likelihood of presence of CMs (P<0.001) (Table 3).

Study variable	Status of congenital malformations		Total
	No CM (controls)	With CM (cases)	
Study year [A]			
2011	854 (33.9) *	277 (33.3)	1131 (33.7)
2012	880 (34.9)	296 (35.6)	1176 (35.1)
2013	788 (31.2)	258 (31.0)	1046 (31.2)
Age of mother (years) - mean ± SD [C]	27.37 (5.00)	28.89 (5.50)	27.75 (5.17)
Age of mother [B]			
<25 years	768 (30.5)	199 (23.9)	967 (28.8)
25-30 years	1137 (451.1)	306 (36.8)	1443 (43.0)
>30 years	617 (24.5)	326 (39.2)	943 (28.1)
Education of mother [B]			
≤secondary education	479 (24.5)	403 (48.5)	882 (31.6)
High school education	852 (43.5)	280 (33.7)	1132 (40.6)
University education	627 (32.0)	148 (17.8)	775 (27.8)
Place of residence of mother [B]			
Urban	1481 (58.7)	425 (51.1)	1906 (56.8)
Rural	1041 (41.3)	406 (48.9)	1447 (43.2)
Employment status of mother [B]			
Unemployed	1026 (52.4)	622 (74.8)	1648 (59.1)
Employed	932 (47.6)	209 (25.2)	1141 (40.9)
Sex of the baby [B]			
Male	1263 (50.1)	519 (63.2)	1782 (53.4)
Female	1259 (49.9)	299 (36.4)	1558 (46.6)
Hermaphrodite	0 (0)	3 (0.4)	3 (0.1)
Gestational age (weeks) - mean ± SD [C]	39.67 (1.26)	38.27 (3.39)	39.32 (2.09)
Weight at birth (grams) - mean ± SD [C]	3375.2 (429.1)	3100.7 (733.8)	3307.9 (533.7)
Total	2522 (75.2)	831 (24.8)	3353 (100.0)

Table 1. Baseline characteristics of the study population Absolute number and column percentages (in parenthesis). For the total, row percentage. Discrepancies with the total number are due to missing information. A P>0.05 according to chi square test. B P<0.05 according to chi square test. C P<0.05 according to students' t test.*

Variable	Year of study			Total
	2011	2012	2013	
Total Tirana births	11181	11456	12860	35497
Total Tirana CMs	277	296	258	831
Total CMs prevalence in Tirana	24.77 *	25.83	20.06	23.41
Type of CM				
Central Nervous System	15 (5.4) – 1.34 †	15 (5.1) – 1.31	6 (2.3) – 0.47	36 (4.3) – 1.01
Eye, ear, face and neck	8 (2.9) – 0.72	15 (5.1) – 1.31	24 (9.3) – 1.87	47 (5.7) – 1.32
Cardiovascular System	68 (24.5) – 6.08	71 (24.0) – 6.20	29 (11.2) – 2.26	168 (20.2) – 4.73
Respiratory System	3 (1.1) – 0.27	3 (1.0) – 0.26	0 (0.0) – 0.00	6 (0.7) – 0.17
Gastro-intestinal system, oral cavity	38 (13.7) – 3.40	42 (14.2) – 3.67	23 (8.9) – 1.79	103 (12.4) – 2.90
Genital system	45 (16.2) – 4.02	54 (18.2) – 4.71	65 (25.2) – 5.05	164 (19.7) – 4.62
Urinary system	10 (3.6) – 0.89	3 (1.0) – 0.26	5 (1.9) – 0.39	18 (2.2) – 0.51
Musculoskeletal system	56 (20.2) – 5.01	57 (19.3) – 4.98	81 (31.4) – 6.30	194 (23.3) – 5.47
Defects of integument	1 (0.4) – 0.09	2 (0.7) – 0.17	0 (0.0) – 0.00	3 (0.4) – 0.08
Chromosomal defects	23 (8.3) – 2.06	18 (6.1) – 1.57	13 (5.0) – 1.01	54 (6.5) – 1.52
Unspecified defects	10 (3.6) – 0.89	16 (5.4) – 1.40	12 (4.7) – 0.93	38 (4.6) – 1.07
Total	277 (100)-24.77	296 (100)-25.84	258 (100)-20.06	831 (100)-23.41

*Table 2. Prevalence and type of congenital malformations in Tirana during 2011-2013. * Prevalence rate per 1,000 live births. † Absolute number and proportional prevalence within all CMs cases (in parenthesis) followed by prevalence rate per 1,000 live births.*

4. DISCUSSION

This study, performed on secondary data retrieved from the National Congenital Malformations Surveillance System (NCMSS) and birth registries in two public obstetric-gynecologic hospitals in Albania, aimed to assess the prevalence rate of CMs and the factors associated with them in Tirana, the capital of Albania. This study is based on all congenital malformations identified among live born infants in public facilities during 2011-2013 in Tirana. This is the first study exploring scientifically the correlates of CMs in Albania and among the very few -national studies reporting on the epidemiology of CMs in this SEE country. Our results suggest that some characteristics of mothers such as age over 30 years, low education, unemployment as well as low gestational age are significantly associated with increased likelihood for the presence of CMs in newborns. In addition, male newborns are almost twice as likely as female newborns to have a congenital malformation. Furthermore, the yearly prevalence of CMs in Tirana was more or less stable during 2011-2013, varying between 20 to 26 CMs per 1,000 live births, with musculoskeletal and cardiovascular systems being most often affected by CMs.

The prevalence of CMs per 1,000 live births reported by our study converge only partially with figures reported by other national studies but are very different compared to international sources reporting data for Albania. For example, previous reports suggested an overall prevalence rate between 14-15 CM cases per 1,000 live births during 2010-2012 in Albania (25, 27) whereas we report prevalence rates varying between 20-26 CM cases per 1,000 live births during 2011-2013 in Tirana. The main explanation for these discrepancies is because of the much more rigorous recording and reporting of CMs in Tirana, the capital of Albania, than in other parts of the country. Because the diagnosis of CMs and their recording and reporting is relatively scarcer in regions of the country other than the capital, then this bias artificially lowers the overall prevalence of CMs in Albania. These challenges have been explored and reported by previous research as well (26, 27). Compared to international information, our figures are much lower. For example, according to March of Dimes the prevalence rate of CMs in Albania is 52.9 per 1,000 live births (1) thus being more than three times higher than our national level calculations (27) and more than two times higher than our prevalence rate in Tirana during 2011-2013. The comparison in these conditions is obviously difficult. However, international figures are based on estimations. For instance, MOD reveals that their figures of CM prevalence around the globe are estimations derived from taking into account the birth prevalence rates of selected birth defects in certain reference populations, global data for common recessive conditions based on WHO guidelines, prevalence of pregnant women of advanced maternal age, rates of consanguineous marriage and national demographic profiles (1). Even though the methodology used is respectable, they still remain approximations of reality. On the other hand, we are very confident about the information on CMs collected for Tirana. Therefore, we think that the true prevalence of CMs in Albania lies somewhere between the figures we report in our study and those reported by MOD.

Variable	Unadjusted models		Multivariable-adjusted models†	
	OR (95% CI)*	P	OR (95% CI)	P
Age of mother B		<0.001 (2) ǂ		<0.001 (2)
>30 years	2.04 (1.66-2.51)	<0.001	2.40 (1.88-3.06)	<0.001
25-30 years	1.04 (0.85-1.27)	0.711	1.42 (1.13-1.80)	0.003
<25 years	1.00 (reference)	-	1.00 (reference)	-
Education of mother B		<0.001 (2)		<0.001 (2)
≤secondary education	3.56 (2.85-4.45)	<0.001	2.03 (1.48-2.78)	<0.001
High school education	1.39 (1.11-1.74)	0.004	1.03 (0.79-1.36)	0.810
University education	1.00 (reference)	-	1.00 (reference)	-
Place of residence of mother B				
Rural	1.36 (1.16-1.59)	<0.001	0.89 (0.72-1.10)	0.282
Urban	1.00 (reference)		1.00 (reference)	
Employment status of mother B				
Unemployed	2.70 (2.26-3.24)	<0.001	2.37 (1.86-3.02)	<0.001
Employed	1.00 (reference)		1.00 (reference)	
Sex of the baby B				
Male	1.73 (1.47-2.04)	<0.001	1.83 (1.52-2.20)	<0.001
Female	1.00 (reference)		1.00 (reference)	
Gestational age (weeks)	0.71 (0.67-0.74)	<0.001	0.80 (0.75-0.85)	<0.001
Weight at birth (grams)	0.99 (0.99-0.99)	<0.001	1.00 (0.99-0.99)	<0.001

*Table 3. Association of congenital malformations with socio-demographic characteristics of the mothers and newborns' parameters; odds ratios (ORs) from binary logistic regression. * OR: Presence of CM vs. lack of CM. † This model was simultaneously adjusted for all covariates presented in the table. ǂ Overall p-values and degrees of freedom (in parentheses). Note: Multivariable-adjusted model is based on 2774 subjects (816 cases and 1958 controls) for whom information on all included variables was available.*

We observed an increasing trend in the prevalence of CMs in Tirana from 2011 to 2012 and then a considerable decrease in 2013. We think that the reason for this sudden decrease might be the increase in diagnosing of CMs during pregnancy and subsequent abortion and the increasingly involvement of private hospitals in carrying out deliveries through the years. Both factors are much more influent in Tirana compared to other regions of the country.

Regarding the overall prevalence of CMs, Albania is ranked among countries with moderate prevalence rates according to MOD (1). The highest prevalence rates were reported in Sudan with 82.0 CM cases per 1,000 live births and the lowest in France with 39.7 cases per 1,000 live births. However, regarding the prevalence of specific CMs our figures are much more comparable to those reported internationally. For example, EUROCAT reported that during 2000-2005 the overall prevalence of congenital heart defect was 7.2 per 1,000 live births, being greater than 10 per 1,000 live births in Austria, Malta, Switzerland, Germany, Poland and Norway (28). Croatia exhibited the lowest prevalence with 5.36 cases of congenital heart malformations per 1,000 births (28), a figure which is very similar to our three-year prevalence of 4.73 cases per 1,000 live births. Across Europe there is a high variability in the prevalence rates of congenital heart malformations with no clear trend distinguishable. The authors suggested that these differences could be attributed mainly to different diagnostic factors being present and employed in different countries (28). Another paper reported the prevalence rates of selected CMs during 1999-2008 in Europe based on EUROCAT data (22). The overall prevalence of congenital heart, musculoskeletal, nervous and genital system defects were 6.05, 0.93, 2.23 and 1.71 cases per 1,000 births (22) (*vs*. 4.73, 5.47, 1.01 and 4.62 cases per 1,000 live births, respectively, in our study). Beside differences in diagnostic factors, the discrepancies might be partially attributed to the cases included in each of the studies since EUROCAT includes also CMs present in fetal or early neonatal deaths, terminations of pregnancy because of fetal anomaly (22, 28) whereas we included only birth defects diagnosed at birth.

Similar to other reports (29, 30), we found that the prevalence of CMs is higher among males than females. Also, similarly to international reports which suggest that low socioeconomic status could be a risk factor for CMs (31, 32), with socioeconomic status being determined by mother's and father's education level and occupation (32), we found that low education level and being unemployed was associated with significantly increased likelihood of having a baby with CM. We also found that older mother's age is a risk factor for CMs, similarly to previous results (33, 34, 35). Even though previous reports did find an association between low birth weight and the risk of CMs (36) we did not find such an association even after controlling for a number of variables. However, the association with gestational age is supported by international literature (37).

Our study has several limitations. Its cross-sectional nature does not allow drawing definite conclusions about the temporality of events. Regarding controls, a part of information on education and occupation level was missing. If this information was available it could have altered the strength of associations we reported in our study. Therefore, our study might suffer from information bias as well. Furthermore, we relied on CM and normal born babies' data retrieved only from the public obstetric-gynecologic hospitals of Tirana and omitted births and CM births which were dealt with in private hospitals because it was not possible to access private hospitals' data. Therefore, our study might also suffer from selection bias, which could affect the prevalence rates we report here. However, the strong point of the present survey is that it included all CM detected at birth in public hospitals in Tirana. This, combined with the fact that the total number of live births in Tirana is an exact figure, allowed us to calculate robust prevalence rates of CMs, which has not been previously reported with such level of accuracy. On the other hand, we also report for the first time about the factors which increase the risk of CMs in Tirana using appropriate controls and adjusting for a number of basic confounders. However, future research is needed in order to calculate national level prevalence rates and to further highlight the role of different factors in the occurrence of congenital malformations in Albania.

CONFLICT OF INTEREST: NONE DECLARED.

REFERENCES

1. Global Report on Birth Defects, 2006, March of Dimes.
2. Birth defects are common. Center for Disease Control and Prevention (CDC). Available at: http://www.cdc.gov/features/birthdefectscommon/. Last accessed: May 2014.
3. Bale JR, Stoll BJ, Lucas AO. In: Reducing Birth Defects: Meeting the Challenge in the Developing World. The National Academies Press. Washington D.C., 2003.
4. Dejmek J, Solansky I, Benes I, Lenicek J, Sram RJ. Air pollution and pregnancy outcome. Environmental Health Perspectives. 2000; 108: 1159-1164.
5. Garcia AM, Fletcher T, Benavides FG, Orts E. Parental agricultural work and selected congenital malformations. Am J Epidemiol. 1999; 149: 64-74.
6. Stemp-Morlock G. Reproductive health: Pesticides and anencephaly. Environ Health Perspect. 2007; 115: A78.
7. Carmichael SL, Shaw GM, Laurent C, Olney RS, Lammer EJ. National Birth Defects Prevention Study. Maternal reproductive and demographic characteristics as risk factors for hypospadias. Paediatr Perinat Epidemiol. 2007; 21: 210-218.
8. Metneki J, Czeizel AE. Increasing total prevalence rate of cases with Down syndrome in Hungary. Eur J Epidemiol. 2005; 20: 525-535.
9. Yang Q, Wen SW, Leader A, Chen XK, Lipson J, Walker M. Paternal age and birth defects: how strong is the association? Hum Reprod. 2007; 22: 696-701.
10. Kazaura M, Lie RT, Skjaerven R. Paternal age and the risk of birth defects in Norway. Ann Epidemiol. 2004; 14: 566-570.
11. Green RF, Devine O, Crider KS, Olney RS, Archer N, Olshan AF, Shapira SK. National Birth Defects Prevention Study. Association of paternal age and risk for major congenital anomalies from the National Birth Defects Prevention Study, 1997 to 2004. Ann Epidemiol. 2010; 20: 241-249.
12. Honein MA, Rasmussen SA, Reefhuis J, Romitti PA, Edward J. Maternal Smoking and Environmental Tobacco Smoke Exposure and the Risk of Orofacial Clefts. Epidemiology. 2007; 18: 226-233.
13. Bille C, Olsen J, Vach W, Knudsen VK, Olsen SF, Rasmussen K, Murray JC, Andersen AM, Christensen K. Oral clefts and life style factors - a case-cohort study based on prospective Danish data. Eur J Epidemiol. 2007; 22: 173-181.
14. Hitchen L. Doctors advise women not to drink any alcohol during pregnancy. BMJ. 2007; 334: 1186.
15. Iveli MF, Morales S, Rebolledo A, Savietto V, Salemme S, Apezteguía M, Cecotti N, Drut R, Milesi V. Effects of light ethanol consumption during pregnancy: increased frequency of minor anomalies in the newborn and altered contractility of umbilical cord artery. Pediatr Res. 2007; 61: 456-461.
16. Krulewitch CJ. Alcohol consumption during pregnancy. Annu Rev Nurs Res. 2005; 23: 101-134.
17. Alcohol and public health (editorial). Lancet. 2005; 365: 1387.
18. Tanner K, Sabrine N, Wren C. Cardiovascular malformations among preterm infants. Pediatrics. 2005; 116: 833-838.
19. Hertrampf E, Cortes F. Folic acid fortification of white flour: Chile. Nutrition Reviews. 2004; 62(6): S44-S48.
20. Griffiths C, Goldblatt P, Fitzpatrick J. Geographic variations in health: main findings and implications for the future. In: Griffiths C, Fitzpatrick J, eds. Geographic variations in health. London: The Stationery Office, 2001: 359-368.
21. The European health report 2005. Major causes of the burden of disease. Available at: http://www.euro.who.int/__data/assets/pdf_file/0004/82435/E87325.pdf. Last accessed: May 2014.
22. Baird PA. Prenatal Screening and the Reduction of Birth Defects in Populations. Community Genet. 1999; 2: 9-17.
23. Loane M, Dolk H, Kelly A, Teljeur C, Greenlees R, Densem J, EUROCAT Working Group. Paper 4: EUROCAT Statistical Monitoring: Identification and Investigation of Ten Year Trends of Congenital Anomalies in Europe. Birth Defects Res A Clinical and Molecular Teratology. 2011; 1: S31-S43.
24. INSTAT Albania. Population and housing census, 2011.
25. Statistical office, Ministry of Health, Tirana, Albania. May 2014 (Unpublished data).
26. Institute of Public Health, Tirana, Albania. May 2014. (Unpublished data).
27. Çanaku D, Merdani A, Gega B, Kakarriqi E. The establishment of congenital malformations surveillance system in Albania – A national necessity. Albanian Medical Journal. 2013; 1: 35-39.
28. Çanaku D, Kakarriqi E, Merdani A, Roshi E. Epidemiology of congenital malformations in Albania during 2011-2012. Albanian Medical Journal. 2013; 3: 56-63.
29. Dolk H. Loane M. Garne E. EUROCAT Working Group. Congenital Heart Defects in Europe Prevalence and Perinatal Mortality, 2000 to 2005. Circulation. 2011; 123: 841-849.
30. Shaw GM, Carmichael SL, Kaidarova Z, Harris JA. Differential risks to males and females for congenital malformations among 2.5 million California births, 1989-1997. Birth Defects Res A Clin Mol Teratol. 2003; 67: 953-958.
31. Raza MZ, Sheikh A, Ahmed SS, Ali S, Naqvi SM. Risk factors associated with birth defects at a tertiary care center in Pakistan. Ital J Pediatr. 2012; 38: 68.
32. Vrijheid M, Dolk H, Stone D, Abramsky L, Alberman E, Scott J. Socioeconomic inequalities in risk of congenital anomaly. Arch Dis Child. 2000; 82: 349-352.
33. Varela MMMS, Nohr EA, Llopis González A, Andersen AMN, Olsen J. Sociooccupational status and congenital anomalies. Eur J Public Health 2009; 19: 161-167.
34. Hagen A, Entezami M, Gasiorek-Wiens A, Albig M, Becker R, Knoll U, Stumm M, Wegner RD. The impact of first trimester screening and early fetal anomaly scan on invasive testing rates in women with advanced maternal age. Ultraschall Med. 2011; 32: 302-306.
35. Reefhuis J, Honein MA. Maternal age and non-chromosomal birth defects, Atlanta–1968–2000: teenager or thirty-something, who is at risk? Birth Defects Res A Clin Mol Teratol. 2004; 70: 572-579.
36. Gill SK, Broussard C, Devine O, Green RF, Rasmussen SA, Reefhuis J; National Birth Defects Prevention Study. Association between maternal age and birth defects of unknown etiology: United States, 1997-2007. Birth Defects Res A Clin Mol Teratol. 2012; 94: 1010-1018.
37. Centers for Disease Control (CDC). Birth defects among low birth weight infants-metropolitan Atlanta, 1978-1988. MMWR Morb Mortal Wkly Rep. 1991; 40: 99: 105-106.
38. Rasmussen SA, Moore CA, Paulozzi LJ, Rhodenhiser EP. Risk for birth defects among premature infants: a population-based study. J Pediatr. 2001; 138: 668-673.