RĪGAS STRADIŅA UNIVERSITĀTE

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EPIDEMIOLOGICAL ASPECTS OF CONGENITAL ANOMALIES AND ASSOCIATED RISK FACTORS IN LATVIA

Summary of Doctoral Thesis

Speciality – Public Health and Epidemiology

Riga, 2013

Doctoral thesis were elaborated in Rīga Stradiņš University (RSU), Public Health and Epidemiology Department

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Presentation of the doctoral thesis will take place on April 8, 2013 at 17.00 on the open meeting of the Promotion Council of Theoretical Medicine disciplines of Rīga Stradiņš University (RSU) in Riga, at Dzirciema Street 16, in the Hippocrate auditorium.

The doctoral thesis is available at the library and home page (www.rsu.lv) of Rīga Stradiņš University.

Elaboration of the thesis was supported by ESF program "Support for Doctoral Students in Obtaining the Scientific Degree in Rīga Stradiņš University".

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CONTENT

INTRODUCTION

Congenital malformations in newborns are one of the major public health problems in Latvia, as well as around the world. They have a leading role in perinatal and infant morbidity and mortality (1-5). The global prevalence is around 2 - 3% of all live births (5-9), nevertheless some studies suggest a prevalence of 3 - 5% (4, 10-12). Congenital anomalies, malformation and pathologies are defined as physical (functional and/or structural) defects at birth may cause by genetic issues, environmental factors, the intrauterine (uterus) environment, chromosomal abnormality and/or factors of other origin that may be diagnosed during prenatal period, childbirth or postnatal period (2-4, 8). Congenital anomalies have been a cause for 24.2% of infant deaths in Latvia during 2011 (13). According to World Health Organization Health for All mortality database (HFA-MDB), the mortality rate for infants under 1 year has increased by 20 % from year 2008 to 2009, 187/100 000 to 221/100 000 respectively. Moreover, infant mortality data of Latvia exceeds the European average indicators for 20 - 40% (152.15/100 000 to 149.25/100 000, respectively). Nevertheless in 2010, the number of infant deaths caused by congenital anomalies has diminished – 121.08/100 000 (14).

Child health largely depends on availability of mother and child health care system, which also includes reproductive and perinatal health care (1, 3). In 2008 Latvia government established improvement in mother and child health care system as top priority for the Ministry of Health, and endorsed this policy by the Medical Treatment Law. New and improved procedures and arrangements to visit directly specialists to undergo preventive and routine medical examination for pregnant women. This amendment help in diagnosing different maternal disease in time, thus directly improving maternal health, reducing birth complications, positively effecting new-born’s health and the health of future babies in Latvia (15).

In Latvia there has been a slight decrease in percentage of women receiving timely antenatal care (until 12th week of the pregnancy). In 2005 around 90% of pregnant women received care but in 2010 it was around 87% (16). Smoking, use of alcohol, narcotics or other addictive substances during pregnancy has a negative effect on the health of the women and on foetal development. Public Health statistics indicates that approximately 10% of labouring women in Latvia have smoked during pregnancy, 0.5% have consumed alcohol, whereas 0.1% have used narcotics (16, 17).

Improvement of mother and child health as well as reduction of infant mortality is one of many goals of the new public health policy "*Public Health Guidelines for 2011 – 2017*" in 2011 (18), the action plan "*Plan for Improving Mother and Child Heath for 2012 – 2014*" developed by the Ministry of Health in Latvia (19) to achieve these goals. The Action Plan provides changes related to the prenatal diagnostics and requires additional medical examinations for pregnant women, including ultrasound screening and necessary tests to facilitate timely diagnosing of congenital anomalies (19, 20).

World Health Organisation database "*Health for All*" (HFA - DB) shows that from 1990 until the beginning of 2000 there has been a rise in the prevalence of congenital anomalies among live both in European region as a whole and in European Union. While from 2000 till 2010, the prevalence for congenital anomalies have dropped both in European region and in European union (21). Indicators characterising the prevalence of congenital anomalies are influenced by many factors, for example the national registration system, termination of pregnancy due to congenital anomalies, prenatal diagnostics, occurrence of risk factors, as well as availability and the quality of health care services (3, 8, 22-24).

To decrease the infant mortality rate, disabilities and complications in birth due to congenital anomalies, primary prevention and improving mother and child health more knowledge is needed. As congenital anomalies are one of

the main causes of infant death and poor health for the children with congenital anomalies, epidemiological research of congenital anomalies is significant for the field of reproductive and perinatal health (4, 30). The field of congenital anomalies among newborn has not been sufficiently studied in Latvia, thus the need for population-based studies of congenital anomalies has been stressed. A literature survey shows earlier clinical research on particular diagnosis of congenital anomalies in Latvia (25-29) but no epidemiological population based studies.

Health Surveys conducted in Latvia are detailed research of more clinical character on sub-groups of specific congenital anomalies or diagnosis in paediatric surgery, dentistry and/or genetics and they do not fully characterise the prevalence of total major congenital anomalies. In Latvia, within the framework of the state research programme "*Scientific Research of Main Malformations Imperilling Latvia's Population Survival and Life Quality by Multidisciplinary Research Consortium*" Project No 6 "*Development of Algorithms Based on Modern Technologies for Diagnostics and Treatment of Congenital Malformations of Children for Reduction of Patient Mortality, Survival Prolongation and Improvement of Life Quality*", the mortality due to congenital anomalies and survival were analysed (31).

Results of these studies indicate both the problems and to-do antenatal foetuses as to minimize births with congenital abnormalities.

This Doctoral thesis aims at finding out latest trends in the live birth prevalence of congenital anomalies and mortality due to congenital anomalies in Latvia, reflecting comparisons between cases and control correlations between frequency indicators and various factors influencing perinatal period, evaluation of congenital anomaly registration in the country, as well as identify problems in existing registration systems. Results of this all study will indicate the problems and the measure to be taken to reduce the risk to be born with congenital anomalies.

Aim of the doctoral thesis: The overall aim of this doctoral thesis work is to gain epidemiological knowledge about the congenital anomalies in new born. Further to investigate the prevalence of the congenital anomalies of live births and mortality due to congenital anomalies among newborn and infants in Latvia, associated antenatal care, mother and newborn health risk factors, as well as assessment of coverage of birth defects registration in the Latvia.

Tasks of the doctoral thesis:

1. To calculate the prevalence of congenital anomalies of live birth, from 2000 till 2010, including break down by diagnose group.

2. To study the association between prevalence of congenital anomalies of live birth and maternal age.

3. To study the influence of newborn congenital anomalies on perinatal and infant mortality from 2000 till 2010.

4. To investigate the effect of health status of a mother, complications during pregnancy and childbearing and other perinatal factors on congenital anomalies of live births.

5. To investigate coverage of prenatal diagnostics and conformity of postnatal diagnosis with the patient medical history data of the Children's Clinical University Hospital, Riga (CCUH).

6. To assess problems and completeness of congenital anomaly registration in Latvia and to develop suggestions for the improvement of congenital anomaly information registration system.

7. To develop suggestions for early identification of pregnant women in risk zone for giving birth to a child with congenital anomalies and identification of newborn in risk zone for congenital anomalies.

Hypotheses of doctoral thesis:

- Changes in prevalence of congenital anomalies are influenced by rise of the mean age of a mother.

- Changes in mortality due to congenital anomalies are affected by general perinatal and infant mortality trends.
- Mothers giving birth to child with congenital anomalies behave more risky towards antenatal care and their own health.
- Congenital anomaly prevalence is influenced by prenatal diagnostics and completeness of registration system in the country.

Scientific novelty of the thesis

To our knowledge this doctoral thesis is the first kind including nationwide cohort study performed to estimate the prevalence of congenital anomaly among all live birth on such a long time period (2000 – 2010), covering all newborn in Latvia including a comparison group without congenital anomalies. Estimating the prevalence and mortality trends and risk factors for congenital anomalies.

Retrospective and cross-sectional cohort analyses were performed by obtaining data from nationwide, population based registers that were inter-linked as follows: **Medical Birth Register** (MBR) that include basic information on prevalence of congenital anomalies at birth, the **National Causes of Death Register** (NCDR) that provides information on all deaths and main cause of death. With an aim to give insight into the congenital surveillance system in country and problems related with the registration of congenital anomalies, new born and infants up till 1 year old treated at **Children's Clinical University Hospital**, Riga (CCUH) during 2003-2008 for congenital anomalies and data of the **Congenital Anomaly Register** (CAR) were linked with MBR.

Live birth prevalence of congenital anomalies is analysed by major congenital anomaly diagnosis groups, it is very important to diagnose these congenital pathologies timely. The timely (prenatal) diagnose of a life threating congenital anomaly is also very helpful in deciding termination of pregnancy

by a pregnant women. As well as to ensure obstetrical and neonatal care appropriate to the condition of a foetus and, if necessary, emergency surgical treatment is also available. In MBR the diagnoses are classified according to The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). These diagnosis codes were correspondingly re-grouped, adapting the methodology of the European network of population-based registries for the epidemiologic surveillance of congenital anomalies (*European Surveillance of Congenital Anomalies - EUROCAT*). That allowed a wider comparison of Latvian national average prevalence of congenital anomalies with EUROCAT average.

Prevalence of congenital anomalies while controlling for risk factors by using multiple logistic regression. This method allowed assessing associations among different risk factors characterising health of a newborn and mother and health-related behaviour with occurrence of congenital anomalies regardless of other risk factors. Differences in the occurrence of risk factors were also studied by making comparisons with the control group. This control group was selected from all healthy newborn not diagnosed with any congenital anomaly or any other health disorder at birth and who were born during the same reference period.

Practical significance of the doctoral thesis

In this doctoral thesis we identified the associations between antenatal factors, maternal and newborn health and prevalence of congenital anomalies at birth. Characterisation of epidemiological situation in Latvia related to congenital anomalies gaves insight into the main problems in the field of diagnostics of congenital anomalies, their registration system and identification and evaluation of potential risk factors. The identification and strength of such risk factors can in turn be used for primary prevention plan.

The information gained from this thesis work can be used in clinical applications by primary health care specialists, gynaecologists, obstetricians and neonatologists. For example, the recommendations on risk factors can be used in a health literacy program for pregnant women in the beginning of their pregnancies. The Epidemiological analyses provides a complete description of the prevalence of congenital anomalies, as well as shows that there are significant differences in the prevalence of various preventable risk factors in cohort of newborn with congenital anomalies, in comparison to healthy children.

The gained knowledge is useful and important for a variety of primary prevention programmes for improvement of perinatal, sexual and reproductive health of Latvian population.

The findings from this doctoral thesis shows presents that the prevalence of congenital anomalies are significantly affected by weaknesses in the existing anomalies in the country accounting systems. In order to provide a complete and high-quality registration system, it is necessary to ensure the inter linking medical birth register with hospital records and Congenital Anomaly Register (CAR). Quality and coverage of the registration can also be improved by training midwifes, gynaecologists and other medical professionals responsible for registering births.

Structure of doctoral thesis

The doctoral thesis is written in Latvian. It consists of 8 sections: introduction, literature review, materials and methods, results, discussion, conclusions, practical recommendations and references. The work consists of 118 pages, including 12 tables and 22 figures. Bibliography consists of 172 references. Doctoral thesis has 7 annexes. There are 6 publications included in this doctoral thesis.

2. MATERIALS AND METHODS

2.1. Data selection

In order to achieve the main aim for this doctoral thesis and to test the hypotheses data from nationwide population-based registers were used. We obtained data from the Medical Birth Register (MBR), National Causes of Death Register (NCDR), Congenital Anomaly Register (CAR), as well as information from the patient medical histories of the Children's Clinical University Hospital (CCUH) on infants hospitalization due to congenital anomalies. Cross-sectional and retrospective case-control study design was used. This research has been approved by the Riga Stradiņš University Ethics Committee.

Main data source MBR was used to estimate the prevalence of congenital anomaly and it was also used to estimate of the association and strength of potential risk factors and congenital anomalies, from 2000 - 2010. The MBR is based on information provided on cards issued to newborns by maternity units across the country. Congenital anomalies included in the analyses were diagnosed by a neonatal doctor using ultrasound examinations and genetic investigation among other methods. These investigations were performed during the time spent in maternity unit after delivery.

According to World Health Organisation's (WHO) definition congenital anomalies, malformation and pathologies are defined as physical (functional and/or structural) defects at birth (2, 3). The diagnosis of congenital anomalies was analysed according to The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10): Q00-Q99 - congenital malformations, deformations and chromosomal abnormalities (32).

The data analysis included all the live births with congenital anomalies during the time period (2000 – 2010). The total number of such live births was 7451, of which 4927 were having major congenital anomalies, see table 2.1.

2.1. Table

Number of live births with congenital anomalies and the proportion of all live births in Latvian (2000-2010)

Year	Live births with CA (n)	%, of live births	Of them with major CA (n)	%, of live births	Control group – live births without CA (n)
2000	548	2.7	414	2.0	13773
2001	707	3.6	493	2.5	12951
2002	723	3.6	464	2.3	13428
2003	797	3.8	516	2.5	14250
2004	767	3.8	414	2.0	13780
2005	761	3.5	457	2.1	15072
2006	718	3.2	492	2.2	16074
2007	747	3.2	481	2.1	16458
2008	633	2.6	436	1.8	17516
2009	584	2.7	413	1.9	13941
2010	466	2.4	347	1.8	11765
kopā	7451	3.5	4927	2.1	159008

Notes: CA – congenital anomalies; n – number of newborn

Congenital anomalies were defined as lethal if the defects cause stillbirth or infant death or pregnancies are terminated after the prenatal diagnosis. They were defined as severe if the defects without medical intervention caused disability or death defects together (8, 33, 34).

Prevalence for the whole time period was calculated for whole all Q diagnosis group (*ICD-10; Q00–Q99*), as well as prevalence for all major congenital anomalies and prevalence of live births by maternal age group. These results were compared with the average prevalence of congenital anomalies in Europe regarding to EUROCAT data. Pathology diagnose codes

for the analysis of the results were re-grouped, adapting the methodology of the EUROCAT (*European surveillance of congenital anomalies*) (35): nervous system (*Q00, Q01, Q02, Q03, Q04, Q05, Q06, Q07*); eye (*Q10.0, Q10.4, Q10.6-Q10.7, Q11-Q15*); ear, face and neck (*Q16, Q17.8, Q18.3, Q18.8*); congenital heart defects (*Q20-Q26*); respiratory system (*Q30-Q34*); oro-facial clefts (*Q35-Q37*); digestive system (*Q38–Q39, Q40.2-Q40.9, Q41-Q45, Q79.0*); abdominal wall defects (*Q79.2, Q79.3, Q79.5*); urinary system (*Q60-Q64, Q79.4*); genital (*Q50-Q52, Q54-56*); limb (*Q65.0-Q65.2, Q65.8-Q65.9, Q66.0, Q68.1-Q68.2, Q68.8, Q69-Q74*); musculo-skeletal system (*Q75.0-75.1, Q75.4-Q75.9, Q76.1-Q76.4, Q76.6-Q76.9, Q77, Q78, Q79.6-Q79.9*); chromosomal (*Q90-Q92, Q93, Q96-99*); other congenital anomalies/syndromes (*Q27, Q28, Q80-Q85, Q89*).

Our Studies cover calculation of prevalence of congenital anomalies, mortality indicators, investigation of associations between odds for congenital anomalies and various factors: maternal age and factors characterising health status of a mother (clinical history, complications during pregnancy and childbirth, abortion history), factors characterising antenatal care (timeliness and having antenatal care); harmful lifestyle of parents (smoking, use of alcohol and psychoactive substances); characteristics of a newborn (gender, birth weight and gestational week).

Number of deaths caused by congenital anomalies was calculated by using the NCDR register. With the aim to find more about prenatal diagnostics of congenital anomalies and registration of diagnoses for live births, the data for a group of hospitalized infants was also analysed. The Medical record of patients with congenital anomalies from CCUH the leading inpatient medical treatment institution in Latvia, providing treatment to newborn and infants with congenital anomalies, was used to achieve this aim.

The first-time hospitalization medical history of 1788 (1605 of them with major congenital anomalies) infant patients with congenital anomalies

(2003-2008) were selected, these infants were one year old at time of hospitalization. The diagnosis at discharge time of this first-time hospitalization was used as the base of analyses.

There were 212 medical histories having records on infant congenital anomaly diagnosed prenatally (mentioned cases were major congenital anomalies), and the data were used for the assessment of diagnostics. Out of the selected 212 histories only 86 had reference to the pregnancy week during which pathology was diagnosed in the ultrasound examination.

In order to assess the completeness of the registration of congenital anomalies at birth (MBR), useful data were only on 629 patients treated by the CCUH, in these cases it was possible data linkage with MBR.

To characterise situation regarding registration of congenital anomalies more in details and conformity of diagnosis in the MBR, additionally also data of the CAR were used (2000 – 2010). Inter-comparison of diagnoses was based on 587 records from the CAR, which were available linkage with MBR. Also within the framework of this analysis, diagnoses of the congenital anomalies were grouped in compliance with the EUROCAT major congenital anomaly sub-groups.

2.2. Definitions and calculations of prevalence and mortality

Total prevalence of congenital anomalies at birth – number of live births and stillbirths (stillbirths after 22nd week of pregnancy and with birth weight 500g) with congenital anomalies per 10 000 births.

Live births prevalence of congenital anomalies – number of live births having congenital anomalies per 10 000 live births.

Cause-specific live births prevalence - number of live births having major congenital anomalies (according to ICD-10 by EUROCAT methodology) in diagnose group per 10 000 live births.

Stillbirths with congenital anomalies – number of stillbirths (stillbirths after 22nd week of pregnancy and with birth weight 500g) having congenital anomalies per 10 000 live births and stillbirths.

Neonatal mortality due to congenital anomalies – number of deaths during neonatal period (0-27 days) due to congenital anomalies per 1000 live births.

Postneonatal mortality due to congenital anomalies – number of deaths during postneonatal period (28 days after births up to 1 year) due to congenital anomalies per 1000 live births.

Perinatal mortality due to congenital anomalies – number of deaths during perinatal period (stillbirths + deaths during first 6 days after birth) due to congenital anomalies per 1000 live births and stillbirths.

Infant mortality due to congenital anomalies – number of live-born deaths during the first year of life due to congenital anomalies per 1000 live births.

Infant death proportion – number of infant deaths caused by congenital anomalies during a certain period of time/total number of infant deaths during this time period *100.

2.3. Statistical analysis

Data necessary for the study were entered and coded in SPSS for Windows 19.0 statistical data processing programme. According to the study objectives, new variables of the categories were developed basing on factors included in the analysis. Total prevalence (incl. live and stillbirths) and live birth prevalence of congenital anomalies and trends in perinatal and infant mortality during the time period from 2000 till 2010 were assessed using linear regression. The χ^2 test was used to compare the subgroups for data analysis in

2x2 tables. The higher χ^2, the higher difference between observed characteristics within groups.

The association between specific risk factors and congenital anomalies among newborn were expressed with odds ratio (OR) (36, 37). OR measure the odds of congenital anomalies of newborns on comparison of factors with newborns in the reference group (healthy newborns). If the OR is greater than 1, the odds for congenital anomaly related to specific factor is greater than in reference group, but if the OR is less than 1, the odds of newborn congenital anomalies in case of this factor are lower, as compared to the reference group. Nonadjusted odds ratio was used to calculate probability of congenital anomalies for newborn in relation to various determining factors, e.g., mother diseases in history, harmful lifestyle factors of parents etc. Moreover, OR calculations were made to analyse association of the maternal age on diagnoses of particular congenital anomalies. Multiple logistic regression was used in cases, when there are several independent variables that can affect the dependant (e.g., maternal age which is related with higher risk of certain congenital anomalies) and it is necessary to match these variables with each other. Odds ratio (OR) was obtained using multiple logistic regression which shows how the increases or decreases the occurrence. The reference value for regression was used healthy newborns (without congenital diagnoses at birth or other diseases, as perinatal period conditions).

Mutual comparison of congenital anomaly coverage and correspondence of diagnoses within the data analysis (MBR with CCUH data, as well as MBR with CAR) was carried out with the help of calculations made basing on similar methodology in another research (38). Coincidence of diagnoses or positive registered cases is equal with number of newborn correctly diagnosed with congenital anomaly in MBR divided by the total number of newborn having congenital anomalies that might have been inter-identified in compared databases (MBR with CCUH; MBR with CAR). Coverage of congenital

anomaly cases or completeness is equal with number of newborn with correctly diagnosed or unspecified congenital anomaly in MBR divided by the total number of newborn having congenital anomalies that might have been inter-identified in compared databases (MBR with CCUH; MBR with CAR). Significance level of 0.05 was selected for all statistical tests. The confidence interval (CI) for estimated results was set to 95%.

3. RESULTS

3.1. Live births prevalence of congenital anomalies and changes from year 2000 to 2010

Medical Birth Register data shows that during the time period from year 2000 to 2010 3.2% (n=7451) of live births were diagnosed congenital anomalies at maternity units. 66.1% (n=4927) of which had major congenital anomalies that are related to serious defects for newborn. Period prevalence of major congenital anomalies among live births is 211.4/10 000 (95% CI 197.4 – 226.2). Overall, prevalence rate has statistically significant decreased – on average by 5.2/10 000 during the years ($p<0.01$) (Figure 3.1.1.).

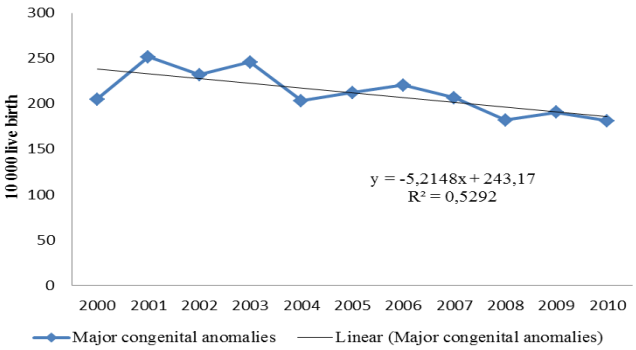

Figure 3.1.1. Trends in live births prevalence of congenital anomalies from 2000 to 2010, per 10 000 live births

The most common anomalies in the structure of major congenital anomalies are congenital heart defects (34.2%), limb anomalies (19.5%) and urinary system abnormalities (13.1%). Also the highest prevalence rate among live births from 2000 to 2010 are related with congenital heart defects, limb and urinary system anomalies. Period live births prevalence of congenital heart defects (Q20 - Q26) is 72.3/10 000 (95% CI 63.8 - 81.2). The prevalence of congenital heart defects has slightly decreased - on average by 2.5 cases, but not statistically significant ($p>0.05$). Total period prevalence of various limb defects of live births is 41.2/10 000 (95% CI 34.9 – 48.2), the prevalence rate has decreased statistically significantl ($p<0.001$) on average by 2.8 cases/10 000 per year. Total period prevalence of congenital urinary system anomalies (Q60 - Q64, Q79.4) is 27.6/10 000 (95% CI 25.5 – 29.7). The prevalence rate of this congenital anomaly subgroup in 10-year period has increased. Prevalence of live births congenital urinary system anomalies in 2010 is 30.3/10 000; 95% CI 23.0 – 39.2) and it has increased on average 1.5 times compared to 2000 (19.3/10 000; 95% CI 13.7 – 26.4), but the increasing trend by 0.3/10 000 per year not statistically significant ($p>0.05$). During the period from 2000 to 2010 the live births prevalence of nervous system congenital anomalies had increased on average by 0.4/10 000 (p,0.05) per year.

3.2. Maternal age and congenital anomalies of newborns

The average maternal age of a newborn with congenital anomalies (2000 – 2010) is 27.7 years (SD 5.8), whereas in control group (healthy newborns) - 26.9 years (SD 5.7). The difference is statistically significant - 0.74 years (95% CI 0.69 – 0.77). There is high correlation ($r=0.8$; $p<0.01$) between maternal age and prevalence rate of congenital anomalies at birth.

Total live birth prevalence of congenital anomalies is 118.1 per 10 000 live births (95% CI 103.7 – 134.0) for mothers up to 19 years of age, 214.5/10

000 (95% CI 106.5 – 297.4) for mothers 20-34 years of age and 261.0/10 000 (95% CI 242.1 – 275.0) – among mother aged 35 years and older. These study results showed an age-related risk for abdominal wall defects, oro-facial clefts and chromosomal anomalies.

Younger mothers (aged under 19) are more likely to have children with cleft lip and cleft palate (OR=1.8), abdominal wall defects (OR=2.0) and chromosomal anomalies (OR=2.4), as compared to mothers aged 20 – 34. While older mothers (35 years and over) has 5 times greater odds for chromosomal anomalies of newborn (OR=5.3) and lower odds (OR=0.77) for heart defects in comparison with live births to mothers in age group 20 – 34.

3.3. Mortality from congenital anomalies and changes from year 2000 to 2010

Mortality analysis of congenital anomalies includes all Q group diagnose codes according to ICD-10 (Q00 – Q99). During the time period from 2000 to 2010 shows that 15.1% (n=368) of all perinatal deaths are related to congenital anomalies, according to the NCDR. Period perinatal mortality due to congenital anomalies is 1.6 (95% CI 1.4 – 1.8) per 1000 live births and stillbirths. Statistically significant decreasing trend during the analyzed time period was observed in both: perinatal mortality associated with congenital anomalies - 0.2/1000 ($p<0.01$) and in total perinatal mortality – 0.5/1000 live births during a year ($p<0.001$) (Figure 3.3.1.).

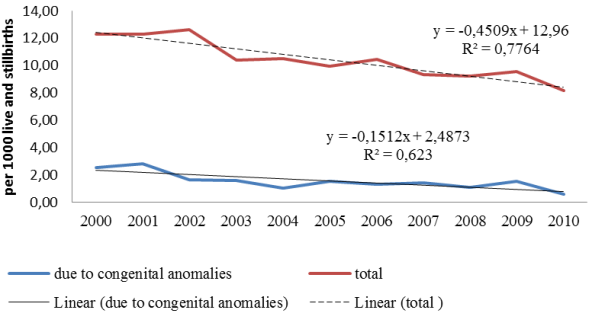

Figure 3.3.1. Trends in total perinatal mortality and perinatal mortality due to congenital anomalies from 2000 to 2010, per 1000 live births and stillbirths

In the congenital anomaly structure of perinatal mortality the highest proportion due to congenital anomalies recorded in the early neonatal period - 25.0% (n=225) with average early neonatal mortality 1.0/1000 live births and stillbirths (95% CI 0.8 – 1.1), respectively - 9.3% (n=143) of stillbirths and stillbirth rate due to congenital anomalies – 0.6 (95% CI 0.5 – 0.7) per 1000 live births and stillbirths.

Congenital anomalies are causing an average 28.4% (n=566) of all infant deaths (2000 – 2010). In 2010 infant death proportion due to congenital anomalies decreased by 9.2 percent points in comparison with 2000.

The decreasing trend of total infant mortality during the analyzed time period is higher than of mortality associated with congenital anomalies (Figure 3.3.2.).

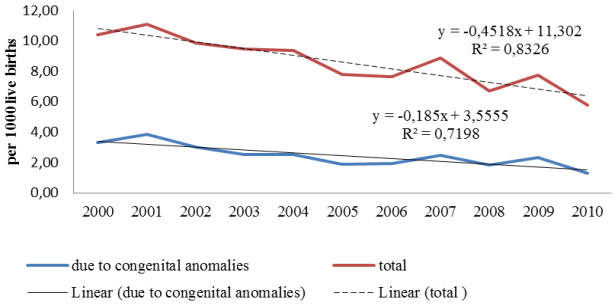

Figure 3.3.2. Trends in total infant mortality and infant mortality due to congenital anomalies from 2000 to 2010, per 1000 live births

Average infant mortality due to congenital anomalies during the time period is 2.4 per 1000 live birth. There is a statistically significant ($p<0.01$) decreasing trend by 0.2/1000 per year. The decrease trend also found for total infant mortality rate - 0.5 cases per year ($p<0.001$). During time period (2000 – 2010) slight decrease ($p<0.05$) was observed also in the structure of perinatal period deaths due to congenital anomalies - 0.8% (95% CI -1.6; -0.2) and in neonatal period deaths – 0.9% (95% CI -1.7; -0.1). Proportion of death associated with congenital anomalies in postneonatal period does not change significantly.

3.4. Associations between congenital anomalies and factors characterising mother and newborn and antenatal care

Within the framework of analysis, various mother and perinatal factors were characterised basing on the total data, including all newborn having congenital anomalies (Q00-Q99), characterising major and minor congenital defects (n=7451). Differences in the occurrence of risk factors was performed with the help of control group that was formed by healthy newborn, which

during the researched time period (2000 – 2010) were not diagnosed with any kind of pathology at birth (n=159008).

Newborn factors

Newborn having congenital anomalies more frequently are born from multiple pregnancies (χ^2=42.5; p<0.001), respectively 2.2% cases (n=162) over 1.3% (n=2050) in control group (see Table 3.4.1.).

3.4.1. Table

Shares in groups of characteristics and odds ratio ($OR_{nonadjusted}$) for newborn having congenital anomalies in relation to newborn factors

Characteristics	CA yes[1]	CA no[2]	χ^2	OR	OR 95%CI
Sex					
boys	54.2	49.1	74.5***	1.2***	1.2; 1.3
girls	45.8	50.9		1.0	
Multiple	2.2	1.3	42.5***	1.7***	1.5; 2.0
Gestational week ≤36	6.6	0.3	4972.4***	24.0***	21.1; 27.3
Birth weight ≤2499 g	6.4	0.6	2834.1***	11.4***	10.2; 12.7

Notes: reference category: healthy newborn (OR=1)
[1] CA yes – case group (newborn having congenital anomalies); [2]CA no – control group (healthy newborn, not having congenital anomalies); *** p<0.001

It was observed that boys have congenital anomalies 1.2 times more commonly than girls. Newborn with congenital anomalies more often are born in preterm birth (OR=24.0), as compared to the newborn having low birth weight (≤2499) (OR=11.4).

Lifestyle factors

Regardless the fact that harmful lifestyle factors of parents medically are poorly documented in medical records, analysis of the data showed that there are statistically significant differences between the groups. Proportion of smokers among mothers giving birth to children having congenital anomalies is

slightly higher (χ^2=6.3; p<0.01), correspondingly 10.1% (n=753), while in control group 9.2% (n=14703). 0.6% (n=45) of women giving birth in the case group and 0.2% (n=336) of the control group have used alcohol (χ^2=48.1; p<0.001). While consumption of psychoactive substances was recorded only in small number of cases, such records had 0.3% (n=20) of unhealthy children mothers and 0.05% (n=75) in control group, (χ^2=61.1; p<0.001).

In relation to the harmful health factors of father, statistically significant differences were observed in the proportions of smokers – 42.9% (n=3197) in the group of newborn with a congenital anomalies and 37.9% (n=60228) in control group (χ^2=76.4; p<0.001). Control group had slightly more notes on the father use of alcohol in medical documentation (χ^2=12.2; p<0.001) – 4.1% (n=6529) over 3.3% (n=245), respectively (see Table 3.4.2.).

3.4.2. Table

Shares of characteristics and odds ratio ($OR_{nonadjusted}$) for newborn having congenital anomalies in relation to lifestyle factors

Characteristics	CA yes[1]	CA no[2]	χ^2	OR	OR 95%CI
Mothers					
used of alcohol	0.6	0.2	48.1***	2.9***	2.1; 3.9
smoking	10.1	9.2	6.3**	1.1	1.0; 1.2
used of psychoactive substances	0.3	0.05	61.1***	5.7***	3.5; 9.4
Father					
used of alcohol	3.3	4.1	12.2***	0.8***	0.7; 0.9
smoking	42.9	37.9	76.4***	1.2***	1.1; 1.3
Used of psychoactive substances	0.1	0.04	2.6	1.9	0.9; 4.6

Notes: reference category: healthy newborn (OR=1)
[1] CA yes – case group (newborn having congenital anomalies); [2]CA no – control group (healthy newborn, not having congenital anomalies); *** p<0.001

Analysis of the nonadjusted odds ratio showed that harmful health factors noticeably increase the odds for congenital anomalies among newborn. Mothers having newborn with congenital anomalies 2.9 times more often have consumed alcohol during the pregnancy (OR=2.9) and on average 5 times more they have used psychoactive substances (OR=5.7). In respect to the harmful health factors of father: 1.2 times more fathers of newborn having congenital anomalies have records on smoking (OR=1.2), if compared to the group of healthy newborn.

Factors characterising antenatal care and health of a mother

Mothers having newborn with congenital defects on average 1.3 times often (χ^2=16.7; p<0.001) have not received antenatal care, i.e., 3.1% (n=232) in case group and 2.4% (n=3769) in control group. Also delayed antenatal care was observed 1.3 times more (χ^2=31.9; p<0.001) for mothers having newborn with congenital anomalies (see Table 3.4.3.).

3.4.3. Table

Shares in groups of characteristics and odds ratio ($OR_{nonadjusted}$) for newborn having congenital anomalies in relation to factors characterising antenatal care and health of a mother

Characteristics	CA yes[1]	CA no[2]	χ^2	OR	OR 95%CI
not received antenatal care	3.1	2.4	16.7***	1.3***	1.2; 1.5
delayed antenatal care	8.9	7.2	31.9***	1.3***	1.2; 1.4
mother diseases in history	33.9	24.4	229.7***	1.6***	1.5; 1.7
pregnancy complications	39.1	38.5	0.95	1.0	0.9; 1.5
delivery complications	44.4	43.1	4.2	1.1	1.0; 1.1
medical abortions in history	1.8	1.5	5.5*	1.2*	1.1; 1.5

Notes: reference category: healthy newborn (OR=1)
[1] CA yes – case group (newborn having congenital anomalies); [2]CA no – control group (healthy newborn, not having congenital anomalies); *** p<0.001

Nonadjusted odds ratios show that, in comparison with the mothers aged under 19, the possibility for newborn congenital anomalies increases along with the age of a mother - from 1.9 (95% CI 1.7 – 2.1) to mothers aged 20-34 to 2.1 (95% CI 1.9 – 2.4) to mothers aged 35 and over.

Mothers having newborn with congenital defects 1.6 times more often had history on various diseases and 1.2 times more medical abortions, as compared to the group of healthy newborn. Whereas odds ratios in relation to the complications during pregnancy and childbirth did not differ statistically significantly between the both groups.

3.5. Results of multivariate analysis in relation to odds for newborn congenital anomalies

With an aim to find out relations among various mother, antenatal and perinatal factors with odds for newborn congenital anomalies, a multivariate logistic regression analysis was performed, mutually matching the characteristics included in the analysis. Analysis was based on multistage multiple logistic regression, forming separate models.

Initially model included also age of a mother, diseases of a mother before pregnancy and during it, as well as pregnancy and delivery complications. Statistical significance of odds ratio remains only for age of a mother ($OR_{adjusted}$=1.16) and illnesses of a mother ($OR_{adjusted}$=1.59), thus further analysis engaged only those factors. Close correlation was observed between newborn gestation age and weight at birth, therefore model included only weight at birth as a factor, such choice is substantiated also by comparison of characteristics prevalence indicators with the share of preterm deliveries (see Table 3.5.1.).

Odds ratio (OR) for congenital anomalies among newborn over control group in relation to factors characterising antenatal care, health of a mother and newborn

Factors		$OR_{adjusted}$ (95%CI)			
	OR_{noadj}	1st model	2nd model	3rd model	4th model
Maternal age ≥35 years	1.21*** (1.12; 1.28)	1.15*** (1.12; 1.23	1.14*** (1.12;1.23)	1.15*** (1.16; 1.24)	1.15*** (1.16; 1.24)
Not received antenatal care	1.32*** (1.16; 1.51)	1.17 (0.98; 1.40)	1.14 (0.96;1.37)	1.15 (0.96; 1.37)	1.02 (0.85; 1.23)
Not received early antenatal care till 12th gestational week	1.27*** (1.17; 1.37)	1.19** (1.19; 1.36)	1.19** (1.17; 1.32)	1.16** (1.14; 1.29)	1.11** (1.10; 1.24)
Mother diseases in history	1.59*** (1.51; 1.68)	1.61** (1.53; 1.70)	1.57*** (1.52; 1.70)	1.57*** (1.49; 1.66)	1.56*** (1.48; 1.65)
Medical abortions in history	1.23* (1.14; 1.47)	1.27*** (1.11; 1.53)	1.27** (1.12; 1.53)	1.27*** (1.15; 1.53)	1.27** (1.15; 1.53)
Mother consumed achocol	2.87*** (2.10; 3.92)	-	2.24*** (1.59; 3.17)	2.36*** (2.21; 6.66)	1.85*** (1.28; 2.68)
Mother use psychoactive substances	5.7*** (3.48; 9.35)	-	3.99*** (2.30; 6.93)	3.83*** (2.21; 6.66)	3,61*** (1,97; 6,26)
Father smoked	1.23*** (1.18; 1.29)	-	-	1.25*** (1.19; 1.31)	1.23*** (1.17; 1.30)
Low birth weight (≤2499g)	11.36*** (10.15; 12.71)	-	-	-	10.49*** (9.21; 11.77)

Notes: reference category covers mothers aged ≤35, have received antenatal care, has early registered for antenatal care (until 12th pregnancy week), no illnesses in history, no medical abortions in history, no harmful life factors of mother and father, weight at birth ≥2500g.

*p<0,05; **p<0,01; ***p<0,001

Gradual supplementation of regression model with various factors did not show notable changes in the OR values. Statistically significant correlations are observed also in total multivariate model after the adjustment of factors in relation to the age of a mother, early antenatal care, mother diseases and medical abortions in history, harmful lifestyle factors of parents and newborn birth weight. The higher odds for congenital anomalies was recorded for low birth weight; still this influence is slightly reducing after adjustment with other characteristics included in the model ($OR_{adjusted}$=10.49), use of psychoactive substances ($OR_{adjusted}$=3.61) and alcohol ($OR_{adjusted}$=1.85) during pregnancy, as well as diseases in medical history ($OR_{adjusted}$=1.56). OR is not statistically significant for antenatal care (was or was not received).

3.6. Associations between total congenital anomalies and different maternal diseases

Mothers having newborn with congenital anomalies in history have more records on chronic or acute diseases, if compared to the group of healthy newborn, correspondingly – 33.9% (n=2173) over 24.4% (n=38827), (χ^2=299.73; p<0.001). Analysis by the disease group covered study on the relation of congenital anomalies with syphilis, other sexually transmitted diseases (including Chlamydia, gonococcus infection, etc. unspecified infections within this diagnose group). Separate investigation included also correlation of the diabetes mellitus with prevalence of congenital anomalies among newborn, researching types I and II, and gestational diabetes, as well as genitourinary tract infections during pregnancy (including kidney, genital etc. unspecified infections within this diagnose group). Less significant odds was observed of other diseases complicating pregnancy and delivery period

(according to the ICD-10 codes: O99), e.g., influence of diseases of endocrine, respiratory, circulatory, digestive system etc.

It was discovered that for mothers with diabetes mellitus odds for newborn having congenital anomalies is on average 6 times higher (OR=6.3; $p<0.001$) than one of mothers not having mentioned disease. Pregnancy diabetes shows 3 times lower relation to congenital anomalies (OR=2.3; $p<0.001$) than diabetes of types I and II.

Sexually transmitted diseases rise the odds for congenital anomalies 2 times (OR=2.0; $p<0.001$), while in the case of syphilis odds ratio increases noticeably – on average 4 times (OR=8.7; $p<0.001$). As regards diseases of genitourinary tract, no notable differences between the groups (mothers having newborn with congenital anomalies and mothers having healthy children) were observed (OR=1.2; $p<0.05$). Odds ratio in relation to various mother diseases complicating pregnancy and delivery period were less significant (OR=1.4; $p<0.001$).

After adjustment by the age of the mother, odds ratio in relation to the disease diagnoses remained at the previous level, except gestational diabetes mellitus – in such cases OR diminished slightly (OR=2.2; $p<0.001$), showing closer correlation between the age of a mother and odds for newborn congenital anomalies.

3.7. Associations between different maternal diseases and particular diagnosis groups of congenital anomalies

To make separate estimate of the mother diseases as a potential risk factor for development of major congenital anomalies, data analysis was based on mother disease as independent characteristics and particular anomaly sub-group – as a dependent one.

Closer relation to separate maternal diseases was observed for seven sub-groups of congenital anomaly diagnosis. Mothers having record on sexually transmitted disease (STD) during pregnancy had 3 times higher odds for newborn to have anomalies of nervous system (OR=3.2; p<0.001), genitals (OR=3.3; p<0.001), chromosomes (OR=3.7; p<0.001), while slightly lower odds ratio was observed for heart defects (OR=2.9; p<0.001) (see Tables 3.7.1.).

3.7.1. Table

Odds ratio (OR) for newborn congenital anomalies in relation to different maternal diseases in history

Congenital anomalies	STD	Diabetes mellitus	Gestational diabetes mellitus	Genitourinary tract infections	Other diseases[1]
Nervous system	3.2*** (1.6; 6.6)	NS	NS	NS	NS
Eye	NS	NS	NS	3.8* (2.1; 10.5)	NS
Heart defects	2.9*** (2.1; 3.7)	4.8** (1.5; 8.3)	2.6** (1.3; 5.3)	NS	1.6*** (1.4; 1.8)
Cleft lip and cleft palate	NS	NS	NS	NS	1.5* (1.2; 2.2)
Urinary system	NS	NS	NS	NS	1.4* (1.2; 1.8)
Genital	3.3*** (1.9; 5.9)	NS	NS	NS	
Chromosomal	3.7*** (1.8; 7.58)	NS	NS	NS	1.8** (1.2;2.6)

Notes: reference category – dont have nav noteiktās slimības anamnēzē
[1]Other diseases (ICD-10; O99); NS – not statistically significant;
*p<0,05; **p<0,01; ***p<0,001

Whereas pregnant women suffering from diabetes mellitus have higher odds ratio for newborn with heart defects (OR=4.8; $p<0.01$). In the case of gestational diabetes mellitus this odds reduces slightly, still it is statistically significant (OR=2.6; $p<0.01$). Genitourinary tract infections in mother history determine higher odds for eye anomalies among newborn (OR=3.8; $p<0.05$). Also other diseases, although slightly, increase odds for congenital defects among newborn from 1.4 to 1.8. Higher possibility for congenital anomalies was observed in following groups: congenital heart defects, cleft lip and cleft palate, urinary system and chromosome anomalies.

3.8. Evaluation of congenital anomaly prenatal diagnostics basing on data of the CCUH patient medical histories

Analysis of the hospital's medical histories indicates that only in 11.9% (n=212) of all studied CCUH patient medical histories that have records on treatment of congenital anomalies (n=1788) (on time period 2003 – 2008) there were note that congenital pathology was diagnosed during prenatal ultrasound examinations. Mentioned notes mainly concerned major congenital anomalies.

Evaluation of the cases diagnosed during ultrasound examinations in particular diagnose group shows that most often antenatal diagnoses concerned urinary system anomalies (renal dysplasia, congenital hydronephrosis etc.) – 27.6% (n=107) (95% CI 23.4 – 32.3) of all hospitalised newborn having urinary system pathologies (n=387) (see Figure 3.8.1.).

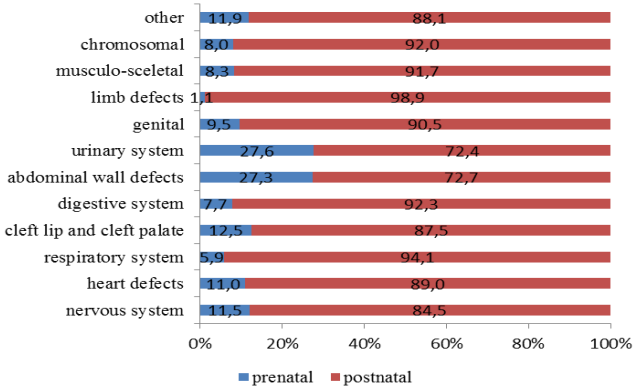

Figure 3.8.1. Diagnostics of most common major congenital anomalies, % (2003 – 2008)

Only in 40.6% (95% CI 34.2 – 47.3) (n=86) of all antenatally diagnosed anomaly cases, on which there was a record in medical document (n=212), there was a note on gestational week, during which ultrasound examination showed pathology. It varied from 21st to 30th gestational week.

3.8.1. Coverage of live-born congenital anomalies in relation to data on patients treated in hospital

Unfortunately only for 1/3 (n=629) of the CCUH hospitalised newborn it was possible to identify the cases and compare them with the MBR.

Diagnose coincidence or number of properly registered cases in the MBR, if compared to the hospital data, comprised 34.8% (95% CI 31.2 – 38.6), in compliance with the formula used in the calculation methodology (219*100/(219+41+369), i.e., (219*100 / 219 (diagnosis of congenital anomaly coincides in MBR and CCUH) + 41 (diagnoses of congenital anomaly differ) + 369 (there was no diagnosis on congenital anomaly in MBR if compared to CCUH data)). Whereas for 38.5% diagnosis was not given in the maternity

units and for 6.5% it initially was other congenital pathology or for 20.2% condition of perinatal period (see Figure 3.8.1.1.).

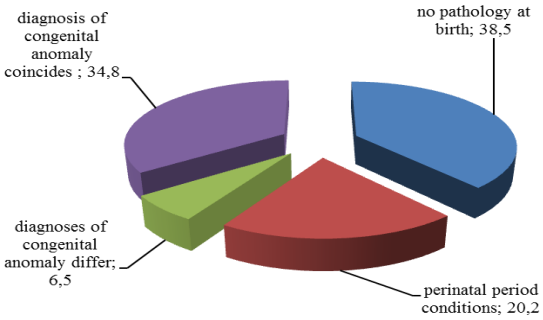

Figure 3.8.1.1. Coverage of live-born congenital anomalies in birth institutions as compared to CCUH data, during the time period from 2003 till 2008, %

Evaluation of the possible completeness of congenital anomalies cases in the Medical Birth Register in comparison with the hospital data shows that it was observed in 41.3% (95% CI 37.6 – 45.2), in compliance with the formula used in the calculations ((219+41)*100/219+41+369), i.e., (219 (diagnosis of congenital anomaly coincide in both databases) + 41 (not specified diagnosis of congenital anomaly in MBR as compared to the CCUH)*100 / 219 (diagnosis of congenital anomaly coincide in both databases) + 41 (diagnosis of congenital anomaly differs) + 369 (there was no diagnosis on congenital anomaly in MBR if compared to CCUH data)). However, when assessing the results, it should be taken into account that CCUH hospitalised cases covered the age under 1 year, thus part of congenital anomalies regards later age that is not reflected in the MBR.

3.9. Coverage of live-born congenital anomaly registration at birth institutions in relation to congenital anomaly register data

Analysis included 587 cases (2000 – 2010) on which information allowing identifying the person was available, and thus it was possible to link the registration systems.

Coincidence of diagnosis or number of properly registered cases in the MBR accounted for 53.8% (95% CI 49.8 – 57.8), in compliance with the formula used in the methodology of calculation (316*100/(316+88+183), i.e. (316*100/316 (diagnosis of congenital anomaly coincides in MBR and CAR) + 88 (diagnosis of congenital anomaly differs in MBR if compared to CAR) + 183 (there was no diagnosis of congenital anomaly in MBR, if compared to CAR)) (see Figure 3.9.1.).

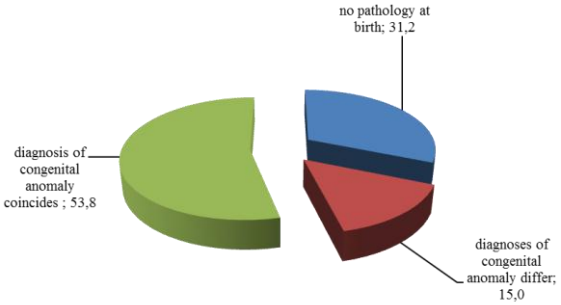

Figure 3.9.1. Coverage of live-born congenital anomalies at birth institutions in comparison with the Congenital Anomaly Register (2000 – 2010), %

Evaluation of the completeness of registered cases in MBR, as compared to CAR, shows that it comprises 68.2% (95% CI 65.0 – 72.4), in compliance with the formula used in the methodology of the calculation ((316+88)*100/(316+88+183)), i.e., (316 (diagnosis of congenital anomaly coincides in both databases) + 88 (MBR has unspecified diagnosis of congenital anomaly)*100 / 316 (diagnosis of congenital anomaly coincides in

both databases) + 88 (diagnosis of congenital anomaly differs) + 183 (there was no diagnosis of congenital anomaly in MBR, if compared to CAR).

The highest share of diagnosis coincidence and more complete registration in birth institutions is related to visual congenital defects, such as cleft lip and cleft palate (61.0%; 95% CI 50.2-70.8) and limb anomalies (76.6%; 95% CI 62.8-86.4). Congenital heart defects (37.5%; 95% CI 26.7-49.7) had the lowest share in diagnosis coverage in the MBR

4. DISCUSSION

Doctoral thesis allowed ascertaining that in Latvia there are problems in registration of congenital anomalies, e.g., there are several mutually unlinked databases, there is no united and complete registration system of congenital anomalies, and that, in turn, interferes epidemiological researches. Therefore, with an aim to get more detailed information of the prevalence of anomalies, within the framework of the study and within the boundaries of possibilities, several systems registering diagnosed cases of congenital anomalies and deaths caused by them, were merged and analysed. Also epidemiological researched conducted in other countries have faced similar problems in relation to the calculations of prevalence data. Similar approach to data analysis is used in finding the completeness of registration and prevalence of pathologies (38-42).

Data of congenital anomaly monitoring system show that in Europe the average period (2000 – 2004) prevalence for live-born comprises 199.3/10 000 (8), whereas period (2000 – 2010) prevalence in Latvia analysed within the framework of the doctoral thesis is slightly higher – 211.4 per 10 000 live births. Evaluation of the five-year period (2000 – 2004) shows that in Latvia prevalence of major congenital anomalies among newborn, if compared to EUROCAT average prevalence, is even higher - 227.5/10 000. Comparatively larger occurrence may be explained with more frequent prevalence of

congenital anomalies among newborn and with hyper-diagnostics of cases in birth institutions, as, after the data are sent to the Medical Birth Register, the diagnoses are not supplemented or changed. However analysis of the study results indicates that in separate diagnosis groups pathologies are not diagnosed in maternity wards, but later, therefore in the Medical Birth Register there is no information on cases diagnosed during postneonatal period.

Regardless the fact that mean age of a mother is increasing (43), the prevalence of newborn congenital anomalies in Latvia during the time period since 2000 has reduced statistically significantly - on average by 5.2 cases annually per 10 000 live births. This finding to some extent conflicts with the discoveries of scientific literature and researches saying that older women have higher risk for having child with congenital anomalies. It has an explanation, because mean age of a mother still falls within the age group under 30 years. As it was proved by the data analysis, females at this age are more careful towards the course of pregnancy: apply for antenatal care earlier, undergo examinations more carefully and pay attention to the treatment and control of diseases.

Prevalence of congenital anomalies among newborn in respect to the age of a mother indicated influence of the age in separate diagnose groups. Younger mothers (aged under 19) are more likely to have children with cleft lip and cleft palate (OR=1.8), abdomen wall defects (OR=2.0) and chromosomal anomalies (OR=2.4), as compared to mothers aged 20 – 34. Whereas, if mother is aged over 35, newborn 5 times more often (OR=5.3) are diagnosed with congenital chromosomal anomalies than children born to mothers aged between 20 and 34. These data meet the findings of other similar researches.

As congenital anomalies is the second most common mortality cause during perinatal and infant age, mortality reduction largely depends on the factors related to this phenomenon. One of the factors considered to be of a great significance is improvement of pathology diagnostics and selection of

most suitable antenatal care (3, 8). Antenatal care is related to favourable outcome of the delivery, diminishing the number of children born pre-term, as well as low weight at birth, thus influencing also infant mortality rate (3, 8, 46). Results of the research indicated that unsuitable antenatal care (mother of a newborn has not applied for antenatal care or did it with delay) has close relation with higher early neonatal mortality (OR=3).

During the time period from 2000 till 2010, perinatal and infant mortality in Latvia both due to congenital anomalies and totally has reduced statistically significantly.

Doctoral thesis covered also evaluation of congenital anomaly potential risk factors. In scientific literature there are researches studying and comparing prevalence of various antenatal and neonatal factors in breakdown by groups – newborn having congenital anomalies and not having pathologies (30, 47). Retrospective analysis of factors characterising antenatal care and age of a mother as well as perinatal factors of newborn in relation to congenital anomalies in Latvia during 11-year period was based on control group – healthy newborn not diagnosed with congenital anomalies or any other perinatal pathologies in maternity units. Multivariate regression model used in the doctoral thesis showed relation with factors covered by the analysis. Nevertheless measured odds ratio in relation with antenatal care and factors characterising health of a mother indicated little differences between the two groups (OR= 1.2 - 1.8), they are statistically significant. It means that analysed risk factor slightly less, but still, increase the odds for newborn congenital anomalies. The closet relation was observed with the birth weight of a newborn (OR=10.4). Such associations is described also in other studies, when comparing newborn with and without congenital anomalies, emphasizing that perinatal mortality increases 7 times (48), while in other research the risk of neonatal mortality is up to 53.1 times higher in a group of newborn having normal weight at birth (≥2500 g), as compared to newborn not having

pathologies, as well as 21.3 times higher risk of neonatal mortality is for pre-term born having congenital anomalies, that, of course, is related not only to prematurity, but also to the type of congenital anomaly (47).

Smoking, alcohol and addictive substances has a negative influence on health of the pregnant, development of a foetus that often is a cause of spontaneous abortion, foetal organ system disorders, premature births, stillbirths and infant mortality during their first week of life (49, 50). Regardless the number of cases having note on harmful life factors of parents registered in the medical documentation is small, data analysis showed some associations. After adjustment the factors (age of a mother, diseases in history, newborn's weight at birth, early antenatal care), higher odds for newborn congenital anomalies was observed with mother's use of alcohol (OR=1.85) and psychoactive substances (OR=3.61). Results of the study show that, during the monitoring of pregnancy and after delivery, particular attention should be devoted to cases having a note on mother's use of alcohol and psychoactive substances, different diseases in mother history and insufficient weight of a foetus. These factors may serve as indicators for the necessity to examine newborn carefully for potential congenital pathology.

One of the pre-conditions for reduction of prevalence of congenital anomalies among live-born is possibly faster diagnosing of disorders in pregnancy and foetal development. Main problem faced in Latvia is rather late discovery of pathologies. As it can be concluded from patient medical records in this study, pathology (anomalies of nervous system, abdomen wall defects etc.) on average is diagnosed during the 28th week of a pregnancy, depending on pathology diagnose group the time varied between 21st and 30th week of a pregnancy. It should be taken into account that in Latvia abortions because of medical indications are performed until the 24th week of a pregnancy. Thus delayed prenatal diagnostics influences also total prevalence indicators, as well as indicates that it is necessary to improve quality of prenatal diagnostics, as

other studies show that early diagnosed neural tube, abdomen defects, chromosome anomalies more often are related to termination of pregnancy. Data show that rates of prenatally diagnosis cases on average in Europe, according to EUROCAT, are rather high, e.g., in relation to gastroschisis – 95%, spina bifida – 81%, Down's syndrome – 72% (51).

Iner-linkage of databases (within the boundaries of possibilities) and analysing coincidence of diagnoses, it turned out that on average in 34.8% - 53.8% diagnoses coincide. Analysis of information on infants having congenital anomalies treated in hospital (in relation to MBR data) showed that in 20% of the cases delivery units had recorded only perinatal period health disorders and in 38% of the cases pathology was not diagnosed at birth; that, of course, is related to short period spent in maternity unit after birth (that most often comprises less than 4 days) and therefore to limited opportunity to observe the newborn and conduct more detailed examination. Likewise there is a part of congenital anomalies, which manifest themselves at a later age.

In research carried out in Australia, when comparing Congenial Anomaly Register information with the genetic centre and children hospital patient data, 54% of cases indicated coincidence of diagnoses (41). Assessment of congenital anomaly completeness in MBR and linking with other databases led to the conclusion that on average 41.3% - 68.2% of congenital anomalies are discovered in delivery units. Comparison of congenital anomaly coverage in breakdown by diagnosis groups shows that most often maternity units register visual congenital defects, whereas the lowest coverage is related to congenital heart defects and chromosome anomalies. Also in other similar research on registration coverage it was found out that most frequently data of the newborn register and birth certificate indicate or have note on visual congenital defects that are more visible (42).

Data on congenital anomalies from Latvian Medical Birth Register has not been widely used before. But this study shows that MBR data may be

useful for epidemiological studies on congenital anomalies in Latvia, as well as by using all live birth cohort-based control group for mutual comparison of potential risk factors. In future, significant factor for using register data (incl. MBR) in research that will ensure and increase epidemiological significance of accumulated information will lay in possibilities to link data with other registration systems in the country. It will improve opportunity for more complete analysis of newborn and infant health in relation to various perinatal factors.

5. CONCLUSIONS

1. During the time period from year 2000 till 2010, prevalence of major congenital anomalies among newborn in Latvia statistically significantly has reduced annually by 5.2/10 000. Breakdown by separate diagnose group shows statistically significant slight reduction only in total prevalence of limb defects – 2.8/10 000 and small rise in congenital anomalies of nervous system – 0.4/10 000.

2. Total congenital anomaly period prevalence (2000 – 2010) among newborn rises along with the age of a mother. For children having congenital anomalies mean age of a mother (27.7 years) is higher than one for children not having pathologies (26.9 years), the difference is statistically significant– 0.74 years.

3. Mothers aged under 19 have higher odds of newborn for cleft lip and cleft palate (OR=1.8); abdomen wall defects (OR=2.0) and chromosome anomalies (OR=2.4), as compared to mothers aged 20 - 34. In comparison with mothers aged 20 – 34, mothers aged over 35 are more likely to have newborn with chromosome anomalies (OR=5.3).

4. During the time period from 2000 till 2010, statistically significant reduction can be observed in both perinatal (of 0.2 cases annually per 1000 live

births and stillbirths) and infant (of 0.2/1000 live births) mortality caused by congenital anomalies, along with decrease in total perinatal (of 0.5/1000 live births and stillbirths) and infant (of 0.5 cases annually per 1000 live births) mortality.

5. Results of the multivariate analysis indicate higher odds ratio (OR) for newborn congenital anomalies in relation to following factors characterising health of a mother and newborn: age of a mother, late antenatal care, mother diseases (syphilis, other sexually transmitted diseases, diabetes mellitus, gestational diabetes, genitourinary tract infections), medical abortions in history, mother's use of alcohol and psychoactive substances, low newborn's weight at birth.

6. Delivery institutions most often and more completely diagnose visual congenital defects of newborn: cleft lip and cleft palate, limb defects, while the most incompletely – congenital heart defects and chromosome anomalies.

7. Prenatal diagnostics of congenital anomalies is delayed - on average during 28^{th} week of a pregnancy.

8. Congenital anomaly total prevalence registration data are influenced by: quality of medical documentation records, incl. specification of approved final diagnosis in registers, as well as late-diagnosed cases of congenital anomalies among infants under 1 year and lack of comprehensive information on termination of pregnancy due to foetus congenital anomalies.

9. Analysis of congenital anomaly prevalence indicators is obstructed by independent work and activities of national databases managed by various institutions and impossible linking of the information available in these databases. Possibilities for inter-linkage would increase the usefulness of accumulated and stored information in research and practical medicine.

Confirmation of hypotheses of the doctoral thesis

First hypothesis that changes in prevalence of congenital anomalies are influenced by rise in mean age of a mother was partially confirmed. Live birth prevalence rates were significantly higher among mothers aged over 35 years. In the same time, there is a reduction in prevalence of congenital anomalies, regardless the rise in mean age of women giving birth.

The second hypothesis that changes in mortality caused by congenital anomalies are influenced by total perinatal and infant mortality trends was partially confirmed. As during the analysed time period perinatal and infant mortality caused by congenital anomalies diminished, also total perinatal and infant mortality dropped. Moreover slight decrease was observed in the structure of congenital anomaly death causes during perinatal and postneonatal period. Still total mortality reduction is faster than mortality caused by congenital anomalies that is rather stable in annual dynamics.

The third hypothesis that mothers having newborn with congenital anomalies act more risky towards antenatal care and own health was proved, as results of the multivariate analysis shows that prevalence of congenital anomalies in association with maternal late antenatal care, mother's diseases in history and mother's use of alcohol and psychoactive substances.

The fourth hypothesis that prevalence indicators are influenced by prenatal diagnostics and completeness of national registration system was confirmed, because analysis data showed that on average 41.3% - 68.2% of congenital anomalies are diagnosed at maternity units.

6. PRACTICAL RECOMMENDATIONS

1. Problems encountered in calculations of congenital anomaly prevalence show necessity to improve national system of congenital anomaly registration:

• by ensuring interlink or reversible exchange of information between the Medical Birth Register and hospitals on confirmation or specification of congenital anomaly diagnosis after discharge from maternity unit (enhancing completion of medical documentation "Supplementary ticket of newborn card" in health care institutions and sending it to the Medical Birth Register);

• by improving linkage between the Medical Birth Register and Congenital Anomaly Register or data exchange on cases of congenital anomalies;

• by developing the Medical Birth Register and accession to the EUROCAT database, with an aim to ensure comprehensive statistical data on Latvia, as well as internationally comparable data and make registration of infant congenital anomaly cases diagnosed during the postneonatal period.

2. Primary health care professionals (general practitioners, nurses) in their preventive work should give information and pay attention to women at reproductive age, education on the harmful lifestyle factors, treatment of chronic and acute diseases, influence of antenatal care on pregnancy outcome, with an aim to improve female knowledge and skills in situations covering issues related to the pregnancy planning.

3. Obstetrical specialists (gynaecologists, midwifes) in situations, when during pregnancy risk factors as mother diseases (diabetes mellitus, sexually transmitted diseases, genitourinary diseases), spontaneous, medical abortions in history, smoking, use of psychoactive substances, insufficient rise in foetus weight are discovered, have to evaluate the results of sonography more

carefully and think about the necessity for additional examination, to eliminate congenital pathologies of a foetus.

4. Neonatologists, pediatricians, and family doctors should devote particular attention in cases, when newborn in birth institutions are diagnosed with conditions of perinatal period that may serve as nonspecific indicators for higher congenital anomaly risk.

5. Within the framework of the public health promotion and education programs on sexual and reproductive health, attention should be directed not only to factors related to contraception, family planning, infertility, but also issues on avoidable risk factors for congenital anomalies and prevention options should be emphasized.

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ACKNOWLEDGEMENTS

Author of the doctoral thesis expresses the deepest gratitude to:

the supervisor - professor Anita Villeruša - for advises and encouraging during whole doctoral studies and progress of the doctoral thesis;

collective of the Riga Stradiņš University Department of Public Health and Epidemiology for friendly support and advises;

work colleagues of the Centre for Disease Prevention and Control for responsiveness and empathy during the progress of work and Centre for the opportunity to use the statistical data for research;

Children's Clinical University Hospital in Riga (int. al. archive) for the opportunity to use the statistical data for research;

and thanks to the family for the support and understanding during the creative process of the study.

Research was conducted in the Riga Stradiņš University Department of Public Health and Epidemiology with the support from ESF National Programme "Support for doctoral programs and postdoctoral research" project "Support for doctoral programs and postdoctoral research in medical sciences" and ESF project "Support for doctoral study programs and research towards a degree in Riga Stradiņš University".