International Clearinghouse for Birth Defects
Surveillance and Research

46th Annual Meeting of the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR)

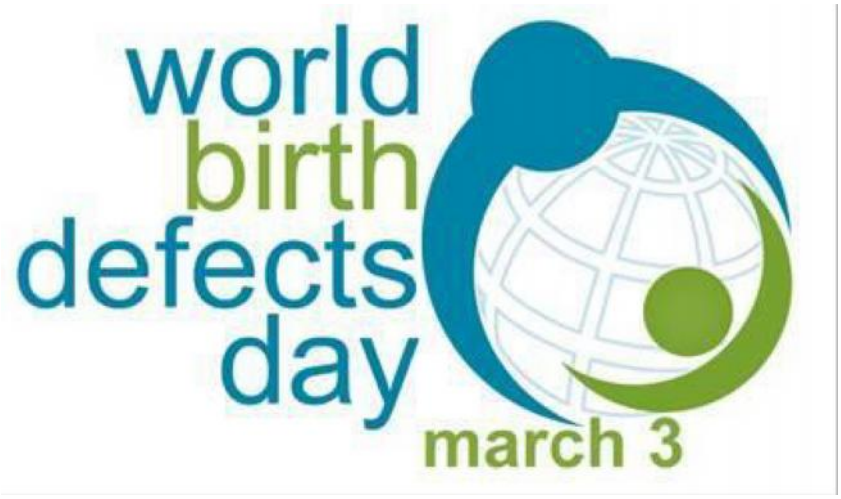
September 8 – 11, 2019
Bratislava, Slovak Republic

Slovak Medical University

Park Inn by Radisson Danube Bratislava (Hotel Danube)

Organized by the ICBDSR and
The Slovak Medical University under the auspices of the Slovak Ministry of Health

The ICBDSR is a Promoting Organization of



www.worldbirthdefectsday.org

Annual Meeting Planning Committee
(in alphabetic order)

Lorenzo D Botto
Boris Groisman
Anke Rißmann
Paul A Romitti
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Acknowledgments

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Peter Šimko, MD, PhD – Rector, Slovak Medical University
Dagmar Zeljenková, MVD, PhD – Dean of Faculty of Public Health, Slovak Medical University
Miroslav Bdžoch, MD, PhD, MPH, Monika Hurná, MD, andAndrea Kálavská MD, PhD, Minister of Health, Slovak Republic

The ICBDSR Executive Committee and ICBD Centre Staff thank all ICBDSR members who work in birth defects surveillance and research, individually as well as in the ICBDSR, to achieve our common goal of primary prevention of birth defects to help ensure that infants worldwide are born healthy.

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Program

Sunday, September 8, 2019 – Hotel Danube	
09:00 – 13:00	Executive Committee Meeting *(Committee Members Only)* (Istropolis Room)
14:00 – 18:00	World Birth Defects Day Partner Organization Meeting (Istropolis Room)
16:00 – 18:00	Meeting Registration
19:30	*Welcome Cocktail at Hotel Danube hosted by the ICBDSR and the Faculty of Public Health, Slovak Medical University* (Hotel Meeting Foyer)

Monday, September 9, 2019 – Slovak Medical University	
08:15	*Bus departure from the Hotel Danube to the Slovak Medical University*
08:30 – 09:00	Meeting Registration
	Opening Session (Building B, Room 001) Moderator: Paul A Romitti
09:00 – 09:30	**Welcome** *Professor Peter Šimko, Rector, Slovak Medical University* *Paul A Romitti, Chair, ICBDSR Executive Committee*
09:30 – 09:50	**ICBD/ICBDSR Update** *Lorenzo D Botto, Director, International Centre on Birth Defects*
09:50 – 10:00	**ICBDSR Distinguished Service Award**
10:00 – 10:45	**J David Erickson Lecture** Program Highlights from the First 25 Years, 1994-2019 *Mark A Canfield, Director, Texas Birth Defects Registry*
10:45 – 11:15	*Coffee break (Building B, Room 134)*
11:15 – 11:30	**Update from the NBDPN** *Paul A Romitti, Director, Iowa Registry for Congenital and Inherited Disorders, Professor, Department of Epidemiology, College of Public Health, University of Iowa*
11:30 – 11:45	**Update from EUROCAT and EUROlinkCAT** *Amanda J Neville, President EUROCAT Association and EUROCAT Registry Leader, Center for Clinical and Epidemiological Research, University of Ferrara*
11:45 – 12:00	**The European Platform on Rare Disease Registration (EU RD Platform)** *Agnieszka Kinsner-Ovaskainen, European Commission, Joint Research Centre, Ispra, Italy*

12:00 – 12:30	**ICBDSR Web-Based Data Platform** *Boris Groisman, Medical Geneticist, Epidemiologist, National Network of Congenital Anomalies, National Center of Medical Genetics, National Administration of Laboratories and Health Institutes, National Ministry of Health and Social development, Argentina*
12:30 – 13:00	**Update on World Birth Defects Day** *Boris Groisman, Medical Geneticist, Epidemiologist, National Network of Congenital Anomalies, National Center of Medical Genetics, National Administration of Laboratories and Health Institutes, National Ministry of Health and Social development, Argentina* *Cara Mai, Health Scientist, U.S. Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities, Division of Congenital and Developmental Disorders, Prevention Research and Translation Branch*
13:00–14:00	*Lunch (Canteen, Building B, Ground Floor)*
14:00– 15:45	**Session I – Oral Communications** (Building B, Room 001) Moderator: Margery Morgan **<u>Prevalence, Descriptive Epidemiology, and Survival I</u>** A multicenter approach to craniosynostosis prevalence and health outcome in central Germany *Anke Rißmann* Prevalence and descriptive epidemiology of congenital hydrocephalus in Iowa, 2000–2016 *Vijaya Kancherla* Congenital anomalies in kidney and urinary tract in newborns: a retrospective study in Bogotá and Cali, Colombia, 2009–2018 *Claudia Milena Orozco* Modelled estimates for selected congenital disorders in South Africa *Helen Malherbe* Prevalence and Mortality among Infants with Congenital Diaphragmatic Hernia: A Multi-Registry Analysis *Wendy N Nembhard*

15:45 – 16:15	*Coffee break (Building B, Room 134)*
16:15 – 18:00	**Session II – Oral Communications** (Building B, Room 001) Moderator: Antonin Šipek Jr **<u>Prevalence, Descriptive Epidemiology, and Survival II</u>** Prevalence of gastrointestinal malformations in 16,958,666 newborns from three surveillance programs from 2011–2015 *Ithzayana Madariaga* Temporal trends and spatial variability of the prevalence of gastroschisis in Arkansas, 1998-2013 *Wendy N Nembhard* Time trends, spatial variation, and risk factors for gastroschisis in Canada, 2006–2017 *Wei Luo* Risk factors contributing to death versus survival of infants with a congenital anomaly: A population-based cohort study of Welsh livebirths using de-identified linked data between 1998 and 2017 *Peter Ho* Trends in perinatal mortality associated with congenital anomalies before and after the introduction of prenatal screening in the Northern Netherlands *Jorieke van Kammen-Bergman*
18:00 – 19:00	**Poster Session** (Room Building B, Room 001)
19:15	*Bus departure from the Slovak Medical University to the Hotel Danube*
20:00	*Dinner at Hotel Danube provided by the Slovak Ministry of Health* (Bratislava Room)

Tuesday, September 10, 2019 – Slovak Medical University	
08:15	*Bus departure from the Hotel Danube to the Slovak Medical University*
09:00 – 10:45	**Session III – Oral Communications** (Building B, Room 001) Moderator: Mary Ann Thomas **<u>Surveillance Methods</u>** An audit of antenatal detection rates in England for 12 specified fetal anomalies, 2016–2017 *Sarah Stevens* Timeliness of data capture and processing in MACDP *Laura J Pabst* Challenges in implementing pulse oximetry screening for detecting congenital heart disease as part of birth defect screening in a middle- and low-income country setting *Nair Madhavankutty Sreehari* A novel software platform for assessing patterns of multiple congenital anomalies *AJ Agopian* The utility of routine hospital admission and mortality data to identify Spinal Muscular Atrophy Type 1 cases in England *Jeanette Aston*
10:45 – 11:15	*Coffee break (Building B, Room 134)*

11:15 – 13:00	**Session IV – Oral Communications** (Building B, Room 001) Moderator: Ieda M Orioli **<u>Risk Factors</u>** Congenital malformations in children born to mothers with diabetes in the Czech Republic in the period 2000–2015 *Antonin Šípek Jr* Recurrent Fetal Arthrogryposis: An Unexpected Diagnosis of Fetal Acetylcholine Receptor Inactivation Syndrome *Mary Ann Thomas* Hospital centered surveillance at birth 2011-2018 and assessment of environmental effectors of changes in reproductive health in Gaza, Palestine, reveals long-term impact of metals weapons-remnants *Paola Manduca* Major birth defects among offspring of Iowa Agricultural Health Study applicators *Paul A Romitti* Maternal MTHFR 677 CT/TT genotype is associated with increased risk of congenital heart defects in offspring *Yevheniya Sharhorodska*
13:00–14:00	*Lunch (Canteen, Building B, Ground Floor)*
14:00 – 15:30	**Annual Business Meeting – Part One** *(ICBDSR members only)* (Building B, Room 2)
15:30 – 16:00	*Coffee break (Building B, Room 2)*
16:00 – 17:30	**Annual Business Meeting – Part Two** *(ICBDSR members only)* (Building B, Room 2)
18:00	*Bus departure from the Slovak Medical University to the Hotel Danube*
	Dinner on your own

Wednesday September 11, 2019 – Slovak Medical University	
08:15	*Bus departure from the Hotel Danube to the Slovak Medical University*
09:00 – 11:00	**Scientific Session I** (Building B, Room 001) Moderator: Michal Dubovicky **Welcome** *Michal Dubovicky, Director, Institute of Experimental Pharmacology and Toxicology, Centre of Experimental Medicine of the Slovak Academy of Sciences* Patients' umbrella organization activities in the field of rare diseases *Beata Ramljaková, Slovak Alliance for Rare Diseases* Ultrasound (pre)postnatal screening of congenital uropoetic defects in Slovakia *Oleksandr Dobrovanov, Professor, St Elizabeth University of Health and Social Sciences* Maternal depression as a threat to children´s health: treat or not to treat it? *Michal Dubovicky, Director, Institute of Experimental Pharmacology and Toxicology, Centre of Experimental Medicine of the Slovak Academy of Sciences* Effects of maternal depression and/or antidepressant treatment on neurobehavioral development of rat offspring *Eszter Bögi, Postdoctoral Scholar, Institute of Experimental Pharmacology and Toxicology, Centre of Experimental Medicine of the Slovak Academy of Sciences*
11:00 – 11:30	*Coffee break (Building B, Room 134)*
11:30 – 13:00	**ICBDSR Collaborative Project Updates and Meetings** (Building B, Room 001)
13:00–14:00	*Lunch (Canteen, Building B, Ground Floor)*

14:00 – 16:00	**Scientific Session II** (Building B, Room 001) Moderator: Michal Dubovicky Rabdomyoma and other tumors of fetal heart at our clinic from 2008 – 2018 *Hana Habánová, I. Gynecology and Obstetric Clinic, Faculty of Medicine, Slovak Medical University* Sjögren's syndrome and pregnancy: Management of the disease and its effect on the fetus *Eliška Lacková,I. Gynecology and Obstetric Clinic, Faculty of Medicine, Slovak Medical University* Cystic and polycystic kidney in the fetus: Management of pregnancy *Michala Harbuláková, I. Gynecology and Obstetric Clinic, Faculty of Medicine, Slovak Medical University* Diagnosis and prognosis of fetuses with CMV infection: Pregnancy management and prognosis *Barbora Gažová, I. Gynecology and Obstetric Clinic, Faculty of Medicine, Slovak Medical University*
16:00	**Annual Meeting Wrap-Up** (Building B, Room 001)
16:15	**Meeting Adjourned**
16:45	*Bus departure from the Slovak Medical University to the Hotel Danube*

Posters (Alphabetical order by presenting author's last name)

A case study of the potential measures taken regarding effective minimization of congenital birth defects in Bangladesh. *Md Ashrafuzzaman, F Zarin, PS Binte Hoque, F Ahmed, A Mimi, FS Laboni, F Rabbi, M Ahsan, A Hanif*

Family outreach activities of the Texas Birth Defects Epidemiology and Surveillance Branch, 2019. *JE Palacios, MK Ethen, MT Le, MT Escobar, MA Canfield*

Polydactyly birth prevalence in the Emilia Romagna Region: Is it increasing? *E Ballardini, A Armaroli, G Astolfi, A Neville, G Cocchi*

Quality of life and social burden associated with surgically correctable congenital malformations in Northern Uganda. *S D'Agostino, B Cigliano, M Ogwang, P Kayma, D Gelormini, M Gelormini, M Bernardele*

Role of information technology, health insurance, and home-based care in improving quality of life, psychosocial framework, and reducing out-of-pocket expenses in a family with a child with birth defects. *A Gambhir, S Gambhir, A Gambhir*

Nephrocalcinosis: Management of maternal and fetal diseases. *E Lacková, M Demes, A Cunderlik, I Rusnak*

Neural tube defects and chronic exposures to low doses of radiation. *W Wertelecki, L Yevtushok, N Zymak-Zakutnia, S Lapchenko, R Shustyk, Z. Sosyniuk, D Akhmedzhanova, I Kuznietsov, L Ostapchuk*

Graph theory as a study means of congenital anomalies associations. *DE Elias, HE Campaña, M Rittler,VR Cosentino, FA Poletta, R Santos, MS Pawluk, LG Gimenez, Ratowiecki, JA Gili, JS Lopez Camelo*

National Registry of Congenital Anomalies in Chile. *C Mellado, RA Pardo, L Velozo*

Perthes (Legg-Calve-Perthes) disease in Wales. *M Morgan, K Janoowala, DF Tucker*

Folate Status in non-pregnant women of childbearing by microbiological assay, in Metropolitan Region, Chile, 2018. *RA Pardo, C Mellado, J López-Camelo, N Nakousi,M Vilca, L Salazar*

Teratology Information System in Vernacular. *E Patskun, S Lapchenko, L Yevtushok, N Zymak-Zakutnia , S Kalynka, D Akhmedzhanova, W Wertelecki*

EUROlinkCAT – Establishing a linked European cohort of children with congenital anomalies – Congenital heart defects requiring surgery: The parent's voice. *A Pierini, K Garne Holm, AJ Neville, G Novelli, A Latos Bieleńska, J Morris, J Clemensen*

Congenital anomalies in children born after assisted reproduction in the Czech Republic: Population-based study. *A Sipek Jr, V Gregor, A. Sipek, J. Klaschka, M. Maly, J. Jirova*

Session I – Oral Communications

Prevalence, Descriptive Epidemiology, and Survival I

Moderator: Margery Morgan

A multicenter approach to craniosynostosis prevalence and health outcome in central Germany
Anke Rißmann

Prevalence and descriptive epidemiology of congenital hydrocephalus in Iowa, 2000–2016
Vijaya Kancherla

Congenital anomalies in kidney and urinary tract in newborns: a retrospective study in Bogotá and Cali, Colombia, 2009–2018
Claudia Milena Orozco

Modelled estimates for selected congenital disorders in South Africa
Helen Malherbe

Prevalence and Mortality among Infants with Congenital Diaphragmatic Hernia: A Multi-Registry Analysis
Wendy N Nembhard

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A MULTICENTER APPROACH TO CRANIOSYNOSTOSIS PREVALENCE AND HEALTH OUTCOME IN CENTRAL GERMANY

C Neusel[1], D Class[2], A Eckert[3], P Goebel[4], R Haase[5], G Jorch[6], L Patzer[7], C Zahl[8], I Schanze[9], A Rissmann[1]

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ICBDSR Registry on which the work is based: Malformation Monitoring Centre Saxony-Anhalt, Germany

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Background and Objectives: Craniosynostosis is the premature closure of one or more sutures of the skull. Usually, these sutures are open to enable passage through birth canal. Sutures are also important for craniofacial growth in the first two years of life. European hospital data showed an increase in the prevalence. The aim of this study was to assess prevalence and time trends of craniosynostosis on a population level in Saxony-Anhalt and analyze the proportion of prenatal diagnosis in these cases.
Methods: For the time period 2000 to 2017, a retrospective multi-center patient cohort study evaluating time of diagnosis was performed via chart review. Hospitalized patients (inpatients and outpatients) diagnosed with craniosynostosis aged less than two years and who underwent surgery from January 1, 2000 to December 31, 2017 were identified at each of the three hospitals. The study included all relevant departments eligible to carry out this type of surgery within the region.
Results: Overall, 91 patients were enrolled in the study. We compared data on these patients with those of 273 controls. There were 75 males and 16 females (ratio 4.7:1). Fifty-one children had isolated craniosynostosis, consisting of 46 with a single-suture and five with a multisuture synostosis. Twenty-nine children had other congenital malformations, and 11 were syndromic. Three cases were diagnosed prenatally, and 34 had skull deformities diagnosed immediately after birth at a mean (SD) age of 3.4 (4.7) months. The mean (SD) age at the time of first admission to a hospital in one of the three surgical centres of Saxony-Anhalt was 5.9 (5.5) months, and 65 patients were operated on at a mean age of 9.1 (6.3) months.
Discussion and Conclusions: For the first time, population-based research on the prevalence of craniosynostosis and its prenatal diagnosis has been conducted for Germany. In contrast to published European reports, we observed a prevalence of 4.8 cases of craniosynostosis/10,000 births that did not increase during the study period. 2000–2016. Although we found a low prenatal detection rate, the diagnosis and treatment in this cohort study seemed timely.

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PREVALENCE AND DESCRIPTIVE EPIDEMIOLOGY OF CONGENITAL HYDROCEPHALUS IN IOWA, 2000–2016

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ICBDSR Registry on which the work is based: Iowa Registry for Congenital and Inherited Disorders, USA

Background and Objectives: Primary congenital hydrocephalus (CH) is characterized by impaired circulation and absorption of cerebrospinal fluid in the ventricular system of the brain, beginning after 20 weeks gestation. CH is a chronic illness, and those affected have disproportionally increased health care expenditures and an increased risk of mortality. There is a paucity of contemporary information on the prevalence of CH and associated factors in the United States. As such, we conducted a retrospective cohort study using data from the Iowa Registry for Congenital and Inherited Disorders (IRCID) to examine the prevalence and descriptive epidemiology of CH.

Methods: We compared IRCID surveillance data for CH cases (n=568) with birth certificate data for Iowa live births (n=663,316) delivered from 2000 through 2016. We used Poisson regression analysis to estimate prevalence per 10,000 live births, Joinpoint regression to examine changes in prevalence, and logistic regression analysis to estimate crude and adjusted prevalence ratios (cPRs and aPRs, respectively) and corresponding 95% confidence intervals (CI)s; aPRs were controlled for selected child and parental characteristics. Analyses examining all CH cases combined were stratified by CH subgroup (aqueductal stenosis, Dandy-Walker malformation, hydrancephaly, other/unspecified [e.g. communicating, noncommunicating, etc.]).

Results: Of the 568 cases, there were 377 other/unspecified, 91 with Dandy-Walker malformation, 88 with aqueductal stenosis, and 12 with hydrancephaly. These cases included 151 (26.6%) isolated, 266 (46.8%) multiple, and 151 (26.6%) confirmed or suspected syndromic phenotypes. Of the 151 syndromic cases, 132 (87.4%) were classified as having a confirmed syndrome, with trisomies being the most common syndrome (40.2%). Among all cases, CH prevalence was 8.56 per 10,000 live births (95% CI=7.89, 9.30) and remained relatively stable over the study period. For all CH cases combined, we observed positive associations for plural pregnancies (aPR=2.04; 95% CI=1.38, 3.02), maternal age at delivery ≥35 years (aPR=1.56; 95% CI=1.09, 2.22), primigravida (aPR=1.34; 95% CI=1.08, 1.66); and non-Hispanic Black paternal race/ethnicity (aPR=1.54; 95% CI=1.03; 2.30). Findings were consistent for some, but not all factors, when examined by CH subgroups.

Discussion and Conclusions: Our estimated prevalence for CH was comparable to other regions of the US. Some, but not all, of our study findings were consistent with previously reported associations with child and parental characteristics, perhaps owing to variations in case inclusion criteria, surveillance methods, and sample size. Future studies are needed to confirm prevalence patterns and associated factors among different CH phenotypes. As our findings are derived from a multi-source, population-based surveillance program, they can inform resource allocation for programs aimed at providing treatment and services to CH cases.

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CONGENITAL ANOMALIES IN KIDNEY AND URINARY TRACT IN NEWBORNS: A RETROSPECTIVE STUDY IN BOGOTÁ AND CALI, COLOMBIA, 2009-2018

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[2]*Institute of Human Genetics, Pontificia Universidad Javeriana, Bogotá, Colombia. Congenital Malformations Surveillance Programme of Bogotá*
[3]*Secretaria de Salud Pública Municipal de Cali, Congenital Birth Defects Surveillance Programme of Cali, Colombia*

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ICBDSR Registry on which the work is based: Colombia, Bogotá: CMSP Congenital Malformations Surveillance Programme and Colombia, Cali: CBDSP Congenital Birth Defects Surveillance Programme

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Background and Objectives: Congenital anomalies of the kidney and urinary tract (CAKUT) are common birth defects in newborns. Previous literature reports 3-6 cases per 1,000 live births and explains 40-50% of the etiologies of chronic kidney disease in children around the world, including structural and functional kidney, collecting system, bladder, and urethral abnormalities. Some pregnancies with CAKUT can end in stillbirth or miscarriage. In newborns, CAKUTs are assoicated with impaired renal function and kidney-related disease in young adults. Generally, CAKUTs can be identified and classified at an early stage of pregnancy with ultrasonography. Owing to the poor outcomes of chronic kidney disease (CKD) in children, it is necessary to know the prevalence of CAKUTs. Our objective was evaluate the epidemiology of CAKUTs, based on data from the Congenital Malformations Surveillance Program (CMSP) in two Colombian cities.
Methods: This is a retrospective study. We obtained information from case-control databases using Latin American Collaborative Study of Congenital Malformations (ECLAMC) criteria. The study included all births and all patients with CAKUTs diagnosed between 2009 to 2018 in two hospitals in Bogotá and three hospitals in Cali. We analyzed sex, prenatal detection, and type of diagnosis among children with CAKUTs. The proportion of each subgroup of CAKUTs and associated malformations were calculated.
Results: There were 137 CAKUTs identified from over 139,300 births, with an average prevalence of 9,8 per 10,000 births. Overall, 71.7% (n=99) were males, and 27.5% (n=39) were females for a sex ratio of 2.5:1. Also, 75.4% (n=104) of cases were recognized prenatally: hydronephrosis 88% (n=103), kidney dysplasia 92% (n=13) and renal agenesis 100% (n=4). The majority, 88%, of births had isolated malformations; 6.5% had other CATKUT-associated defects.
Discussion and Conclusions: CAKUT prevalence was variable in different reports. In our study, our prevalence was 9.8 per 10,000 births, much lower than in other studies (Birth Defects Monitoring Program BDMP 70 per 10,000 births and EUROSCAN 16 per 10,000 births). We found a high proportion of CAKUTs was reported in male newborns and the majority were isolated malformations. The most frequently detected subgroup of CAKUTs was hydronephrosis, similar to other reports. Given the impact on the quality of life of complications secondary to CAKUT, it is very important that the diagnosis is timely for proper follow-up and intervention.

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MODELLED ESTIMATES FOR SELECTED CONGENITAL DISORDERS IN SOUTH AFRICA

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ICBDSR Registry on which the work is based: Not Applicable

Background and Objectives: Congenital disorders (CDs) remain an unprioritized healthcare issue in South Africa (SA). Although an estimated 1/15 live births (6.8%) are affected by CDs in SA, national surveillance is underreporting by 98%. The lack of empiric data on CDs is preventing informed policy decision-making for service planning at all levels. This underreporting perpetuates capacity and infrastructure shortages, resulting in misdiagnosis and non-diagnosis of CDs and misclassification of CD-related deaths and preventing those surviving with CDs from accessing the care they require. Modelling offers a reliable means of estimating CDs until surveillance systems are adequately developed. This study quantified the CD burden of disease at a national and provincial level using the Modell Global Database of Congenital Disorders (MGDb). In SA, child mortality rates have stagnated since 2011, and undertaking this modelling exercise for 2012 provides a baseline for comparison with future modelled data from subsequent years.
Methods: In this study, methods adapted from the MGDb and birth prevalence data from well-established surveillance systems were used with local demographic data to generate 2012 baseline birth prevalence estimates for early-onset endogenous CDs in the absence of care. The 2012 actual birth prevalence was estimated using the MGDb approach to evaluate the effect of current interventions. Access to relevant health services (including initial diagnosis and treatment) and the impact of interventions was quantified using the infant mortality rate (IMR) as a proxy. Four groups of early-onset CDs (presenting before the age of 20) with known baseline birth prevalence rates were included: single gene disorders, chromosomal disorders, malformations (non-syndromic, isolated), and additional conditions. CDs due to post-conception environmental causes, genetic risk, and late onset disorders were excluded.
Results: Total birth prevalence for baseline (no care) estimates was 30.4 per 1,000 live births. Of the 37,280 births affected, 6% were stillborn and over one-half (56%) died under age 5 from CD-related causes, with all survivors disabled. In 2012, access to care was estimated at 31% nationwide, reducing birth prevalence to 29.2 per 1,000 live births. An estimated 2,580 (7%) of affected births were avoided through pre-pregnancy/prenatal interventions. Survival increased by 14% with 3,810 more children living to age 5. Of the 18,070 survivors, 29% were effectively cured, and 12,780 (71%) survived with disability. The number of affected births per province was proportional to overall births occurring in each, for baseline and actual estimates. Estimates for access to care ranged from 93% (Western Cape) to 18% (Free State), resulting in a unique ratio of actual outcomes per province. The greatest impact of services was in Western Cape, and the least impact in Free State and KwaZulu-Natal.
Discussion and Conclusions: This study: 1) quantified the baseline scale of the burden of a subset of early-onset endogenous CDs in SA for 2012; 2) modelled estimates for access to 30% available care, demonstrating proportional changes in birth outcomes made possible by care; and 3) enabled an estimate of the effect of services. A much higher proportion of births affected by CDs is indicated than is currently documented by national CD surveillance. The MGDb approach is a tool to inform policy makers, providing conservative, interim estimates until surveillance improves and empirical data become available. While baseline estimates are strongly evidence-based, the calculations for the outcome estimates of this approach are less reliable, and the source of quality, local demographic data is essential. Further study includes analyses of modelled estimates for: (a) specific CDs; (b) specific provinces of SA; (c) costing of specific interventions; and d) repeated modelling at appropriate intervals.

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PREVALENCE AND MORTALITY AMONG INFANTS WITH CONGENITAL DIAPHRAGMATIC HERNIA: A MULTI-REGISTRY ANALYSIS

MD. Politis[1], E Bermejo Sánchez[2], MA Canfield[3], P Contiero[4], JD Cragan[5], S Dastgiri[6], HEK de Walle[7], M Feldkamp[8], A Nance[9], B Groisman[10], M Gatt[11], A Benavides Lara[12], PM Hurtado Villa[13], K Kallén[14], D Landau[15], N Lelong[16], JS Lopez Camelo[17], L Martinez[18], M Morgan[19], OM Mutchinick[20], A Pierini[21], A Rissmann[22], A Šípek[23], E Szabova[24], W Wertelecki[25], I Zarante[26], MK Bakker[27], V Kancherla[28], P Mastroiacovo[29], WN. Nembhard[1]

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ICBDSR Registry on which the work is based: 25 ICBDSR members registries

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Background and Objectives: Congenital diaphragmatic hernia (CDH) is a severe birth defect with a high mortality rate. The aim of this study is to examine the global prevalence and mortality trends associated with CDH.

Methods We used data from twenty-five hospital- and population-based surveillance programs in 19 countries from members of the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) for a birth defects surveillance study between the years 1974 and 2015. Cases were infants with CDH that resulted in live births, stillbirths, or elective termination of pregnancy for fetal anomalies. In programs where data were available, we examined mortality by isolated and non-isolated case status (the latter including multiple congenital anomalies and syndromic cases combined). Prevalence and Kaplan-Meier mortality rates were calculated for all births, by each country, and by type of registry.

Results: The total prevalence of CDH between the years 1974 and 2015 was estimated to be 2.7 per 10,000 total births (95% Confidence Interval: 2.6, 2.8). Overall, the cumulative percent mortality of CDH was 37.2%, with hospital-based registries having a higher number of live births with CDH resulting in death than population-based registries (45.1% compared to 33.6%). Multiple and syndromic cases of CDH had higher one-week mortality rates (44.9%) than isolated cases (28.4%) for both hospital- and population-based registries. The highest proportion of deaths due to CDH occurred among infants aged 2 to 6 days for both registry types (36.3% for hospital-based and 12.1% for population-based).

Discussion and Conclusions: Our findings show that the global prevalence of infants with CDH remains high, with an elevated mortality rate, especially during the first week of life. A major concern is the clinical presentation of CDH and its association with other anomalies which may indicate a specific etiologic or genetic cause. Further research is needed to examine the differences between population- and hospital-based registries and the 'hidden mortality' that might be present.

Session II – Oral Communications

Prevalence, Descriptive Epidemiology, and Survival II

Moderator: Antonin Šipek Jr

Prevalence of gastrointestinal malformations in 16,958,666 newborns from three surveillance programs from 2011–2015
Ithzayana Madariaga

Temporal trends and spatial variability of the prevalence of gastroschisis in Arkansas, 1998-2013
Wendy N Nembhard

Time trends, spatial variation, and risk factors for gastroschisis in Canada, 2006–2017
Wei Luo

Risk factors contributing to death versus survival of infants with a congenital anomaly: A population-based cohort study of Welsh livebirths using de-identified linked data between 1998 and 2017
Peter Ho

Trends in perinatal mortality associated with congenital anomalies before and after the introduction of prenatal screening in the Northern Netherlands
Jorieke van Kammen-Bergman

International Clearinghouse for Birth Defects
Surveillance and Research

PREVALENCE OF GASTROINTESTINAL MALFORMATIONS IN 16,958,666 NEWBORNS FROM THREE SURVEILLANCE PROGRAMS SINCE 2011 TO 2015

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ICBDSR Registry on which the work is based: Colombia, Bogotá :CMSP Congenital Malformations Surveillance Programme, and , Colombia, Cali: CBDSP Congenital Birth Defects Surveillance Programme

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Background and Objectives: Gastrointestinal malformations (GM) are defined as any structural congenital anomaly of the gastrointestinal tract. GM have an impact on infant morbidity and mortality and most require surgical treatment. Our objective is to describe GM prevalence reported in three Surveillance Programs: National Birth Defects Prevention Network (NBDPN), National Network of Congenital Anomalies of Argentina (RENAC) and Bogota and Cali Congenital Malformations Surveillance Programme (CMSP) between 2011-2015.

Methods: We reviewed 586,786 births in the CMSP, 1,316,374 births in the RENAC and 15,348,899 in the NBDPN from 2011 to 2015. Data were obtained from each program's online databases and the prevalence per 10,000 births were calculated with their respective confidencie intervals (CIs) using the Poisson Method. We selected cases with oesophageal atresia/stenosis with or without fistula (OA), small intestine atresia/stenosis (SIA), anorectal atresia/stenosis (AA), diaphragmatic hernia (DH), omphalocele and gastroschisis.

Results: Overall, 33,443 cases of GM were reported from a total population of 16,958,666, establishing a prevalence of 19.72 per 10,000 births (95% CI: 19.51-19.93). We observed differences in GM frequencies among the surveillance programs, SIA was the most frequent GM, followed by gastroschisis in the CMSP; gastroschisis had the highest prevalence in the RENAC and NBDPN.

Discussion and Conclusions: Congenital anomalies are common, costly, and critical. In our country, GM represent the fourth leading congenital anomaly. We observed significant prevalence variation among GM in the three surveillance programs. Those differences could be explained by national coverage (NBDPN and RENAC) versus local coverage (two cities in CMSP), each surveillance strategy, and intrinsic factors to each country (nutrition, socioeconomic status, exposition). The high prevalence of gastroschisis in the RENAC program is striking. There are interesting differences in the GM prevalence between surveillance programs. This can be explained by methodological reasons or intrinsic factors in each country. It is important to carry out studies of risk factors related to these malformations to understand the differences between the countries and in this way to propose prevention strategies.

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TEMPORAL TRENDS AND SPATIAL VARIABILITY OF THE PREVALENCE OF GASTROSCHISIS IN ARKANSAS, 1998-2013

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ICBDSR Registry on which the work is based: Arkansas Reproductive Health Monitoring System

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Background and Objectives: A report based on data from 14 United States (U.S.) state birth defect surveillance programs described a 30% increase in the prevalence of gastroschisis (from 3.6 per 10,000 live births in 1995–2005 to 4.9 in 2006–2012) and urged researchers to further investigate the etiology of this increase. Arkansas is an important state since it had the highest prevalence of gastroschisis in a national study based on 15 U.S. states (1995–2005). Our objective was to explore trends in prevalence and the spatial distribution of gastroschisis in Arkansas between 1998 and 2013.

Methods: Infants with gastroschisis, born 1998-2013, were obtained from the Arkansas Reproductive Health Monitoring System (ARHMS), a statewide birth defects registry that monitors live births, fetal deaths and terminations for structural birth defects. Birth record data were obtained from the Arkansas Department of Health. Data from the US Census Bureau and Arkansas Department of Environmental Quality were used for county characteristics. Maternal residence at delivery was geocoded for spatial analyses. Annual prevalence rates by county and region were calculated and Joinpoint regression analyses were used to assess temporal trends. Spatiotemporal cluster detection methods were used to identify counties with unusually high prevalence rates. Poisson regression was used to calculate crude and adjusted prevalence ratios. Covariates included individual and county level maternal race/ethnicity, age, education, poverty and county level body mass index (BMI) and agricultural characteristics.

Results: We identified 357 cases of gastroschisis among 617,404 live births. The overall prevalence of gastroschisis ranged from 3.0 per 10,000 live births in 2001 to 9.1 in 2012 (overall prevalence=5.8). We observed an annual increase of 4.7% (P=0.0001) in the prevalence of gastroschisis during the study period. A high overall prevalence (range: 15-20) was noted in 5 counties. During the study period, prevalence increased in 48 counties and decreased in 3 counties. Both Emerging Hot Spot Analysis (EHSA) and SaTScan detected one overlapping spatiotemporal cluster of gastroschisis cases in the western part of Arkansas. EHSA identified a 3-county cluster in 2013 and SaTScan identified an 18 county cluster between 2006 and 2013. Multivariable Poisson regression models for each cluster were found to be statistically significant but did not identify any individual or county factors that explained the temporal trends or spatiotemporal clusters. Hog farming emerged as a factor of interest.

Discussion and Conclusions: The prevalence of gastroschisis in Arkansas increased during the study period and varied by county and region. Spatiotemporal analysis suggests a possible cluster of gastroschisis in Western Arkansas. The etiology or factors associated with the increasing prevalence over time and spatiotemporal differences within the state remain unknown. Future studies will explore hog farming and its potential association with these clusters.

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TIME TRENDS, SPATIAL VARIATION AND RISK FACTORS FOR GASTROSCHISIS IN CANADA, 2006 TO 2017

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ICBDSR Registry on which the work is based: Canadian Congenital Anomalies Surveillance System (CCASS)

Background and Objectives: Gastroschisis is a congenital malformation characterized by a defect of the abdominal wall, exposing the viscera. Its cause is largely unknown, although there is a strong association with young maternal age. Several previous studies have shown increases in rates of gastroschisis in various countries, including Canada. We carried out a study to examine recent temporal trends and spatial variation in gastroschisis prevalence and associated maternal and infant characteristics in Canada.

Methods: The study included all hospital-based live births in Canada (excluding Quebec) between April 2006 and March 2018, with information from the Canadian Institute for Health Information (a data source for the Canadian Congenital Anomalies Surveillance System). Temporal trends by maternal age, region of residence, maternal and infant characteristics and pregnancy outcomes were quantified using prevalence rate ratios (RR) and 95% confidence intervals (CI). Multivariable Poisson regression was used to quantify the independent association between different risk factors and gastroschisis.

Results: Over the period 2006 to 2017, the proportion of mothers aged 20-24 years declined from 16.5% to 11.2%. The proportion aged <20 years halved, from 4.7% to 2.2%. Gastroschisis rates decreased from 3.78 to 2.79 per 10,000 live births (P-value for trend <0.001). While the prevalence of gastroschisis among the offspring of women aged <20, 20-24, and 30-49 years remained largely unchanged, an increasing rate was observed in the offspring of women aged 25-29 (P<0.01). The overall age-adjusted rate of gastroschisis showed a nonsignificant increase (adjusted annual average change in prevalence ratio 1.004, 95% CI 0.989, 1.020). Women in the Yukon, Northwest Territories, and Nunavut had an over 4-fold higher prevalence rate of gastroschisis compared with the rest of Canada (RR 4.27, 95% CI 3.08, 5.92). In multivariable analyses, women aged <20 years had the highest risk of having a gastroschisis-affected infant (RR 7.93, 95% CI 6.64-9.47 compared with women aged 25-29 years).

Discussion and Conclusions: Problematic substance use (RR 1.89, 95% CI 1.35-2.64), tobacco use (RR 1.74, 95% CI 1.14-2.65), rural residence (RR 1.29, 95% CI 1.12-1.48) and residence in the three territories (RR 2.15, 95% CI 1.62-3.78) were associated with a higher risk of gastroschisis. Women with diabetes mellitus had a lower risk of gastroschisis compared with women without diabetes (RR 0.36, 95% CI 0.21-0.61). Gastroschisis prevalence did not differ by infant sex, parity or plurality. The prevalence may have decreased because there are less young mothers (<25 years), and younger mothers are associated with higher rates of gastroschisis.

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RISK FACTORS CONTRIBUTING TO DEATH VERSUS SURVIVAL OF INFANTS WITH A CONGENITAL ANOMALY: A POPULATION-BASED COHORT STUDY OF WELSH LIVEBIRTHS USING DE-IDENTIFIED LINKED DATA BETWEEN 1998 AND 2017

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ICBDSR Registry on which the work is based: Congenital Anomaly Register and Information Service (CARIS), Wales, UK

Background and Objectives: Congenital anomalies are the second leading cause of infant death in the UK, accounting for over one-third of all infant deaths. To date, population-based studies of risk factors for mortality of infants with congenital anomaly have been limited. Estimates of infant mortality associated with congenital anomalies are important to inform planning of healthcare and social interventions aimed at reducing infant mortality. Congenital Anomaly Register and Information Service (CARIS) is a high-quality, population-based register established in 1998 to identify congenital anomalies in all regions of Wales and is known to have high reporting rates due to a robust surveillance system. CARIS collects data about congenital anomalies involving structural, metabolic or genetic defects, present before the end of pregnancy. The aim of this study was to investigate the nature, clinical features, and risk factors associated with the risk of infant death versus survival in infants with congenital anomalies.

Methods: A population-based cohort study was conducted using registry data from CARIS with linkage to data on livebirths and deaths from the UK Office for National Statistics. The study population included all livebirths with birthweight ≥500g, gestational age ≥22+0 weeks, and a diagnosis of a congenital anomaly between 1998 and 2017. The characteristics explored were socio-demographic, maternal, infant, and intervention factors. Univariable logistic regression was performed to obtain crude odds ratios; those with $p<0.1$ were explored in a multivariable model. Multivariable logistic regression was performed using a backward stepwise approach to obtain adjusted odds ratios, and a subsequent likelihood ratio test to examine the independent effect of each significant variable; $p<0.05$ was considered significant in the final model. The analysis was performed separately for: infants with any anomaly; those with isolated anomalies; those with multiple anomalies; and those with cardiovascular anomalies.

Results: Overall, 30,424 livebirths affected by congenital anomalies were identified, of which 20,008 (65.8%) had isolated anomalies and 10,374 (34.1%) had multiple anomalies. Cardiovascular anomalies contributed the highest infant mortality rate (IMR: 1.33 per 10,000 livebirths) among isolated anomalies. Significant increases in adjusted odds of infant mortality were found among infants born to mothers of non-White vs White ethnicity (aOR 2.25; 95% CI: 1.77-2.86); parous vs nulliparous (aOR 1.24; 1.08-1.41); active smokers during pregnancy vs non-/ex- smokers (aOR 1.20, 1.02-1.40); preterm vs term (aOR 4.38; 3.86-4.98); and female vs male infants (aOR 1.28; 1.13-1.46). Infants who required surgery in the first year of life had a lower odds of infant mortality than those who did not (aOR 0.80; 0.68-0.95). Preterm birth was a significant risk factor for all anomaly types but the effect of the other characteristics varied according to the anomaly group.

Discussion and Conclusions: Socio-demographic, maternal, infant, and intervention factors have a significant impact on infant mortality in babies with congenital anomalies by different potential mechanisms depending on the type of anomaly. For example, the excess mortality from congenital anomalies in minority ethnic groups may be due to an interplay of factors resulting in unequal access to antenatal screening and medical and surgical interventions, different attitudes toward congenital anomalies and termination of pregnancy, and consanguinity. Likely smoking-related mechanisms include placental abruption and an increased risk of sudden infant death syndrome. Prematurity increases the risk of comorbidities and related complications. Infants with an anomaly who required surgery in the first year of life had a lower risk of death compared to those who did not or whose anomalies were too severe for

surgery.

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TRENDS IN PERINATAL MORTALITY ASSOCIATED WITH CONGENITAL ANOMALIES BEFORE AND AFTER THE INTRODUCTION OF PRENATAL SCREENING IN THE NORTHERN NETHERLANDS

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ICBDSR Registry on which the work is based: Northern Netherlands

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Background and Objectives: In 2008, Euro-Peristat published a report on perinatal health in 2004 that showed that perinatal mortality in the Netherlands was among the highest in Europe (10.5 per 1,000 births). After publication of the report, several actions were implemented in Dutch obstetric care to reduce perinatal mortality. In 2007, a nationwide prenatal screening program was implemented in the Netherlands. In 2015, the perinatal mortality rate dropped to 7.8 per 1000 births. However, a limitation in the interpretation of these rates is that no distinction could be made between natural fetal deaths and induced abortions. We set out to study trends in perinatal mortality associated with congenital anomalies (CA), to determine the impact of early detection of CA on perinatal mortality in a period before and after the implementation of a prenatal screening program in the Northern Netherlands.
Methods: We included all children and fetuses with CA registered in the Eurocat Northern Netherlands database with a pregnancy end date from 2001-2015. For each child or fetus, we used information on birth year, pregnancy outcome, death date, gestational age at birth or termination, time of detection of CA, and type of CA. Fetal mortality was classified as ≤22 weeks or >22 weeks gestation and as natural or induced (termination or pregnancy). Perinatal mortality was defined as combined fetal mortality >22 completed weeks gestation and early neonatal mortality (0-6 days after birth). Data from the Central Bureau of Statistics on the number of live births, stillbirths, and neonatal deaths in the registration area of Eurocat Northern Netherlands were used to calculate mortality rates associated with CA. We examined trends in perinatal mortality rate and contribution of subtypes to total mortality for all CA and specific CA over the study period.
Results: Total mortality among cases with CA increased (14.1% in 2001 to 21.2% in 2015), mainly due to an increase in induced fetal mortality ≤22 weeks, (2.9% to 11.7%). Perinatal mortality (fetal deaths >22 weeks and early neonatal mortality) was stable (6.1%), but there was a shift from neonatal to fetal mortality (increase in fetal mortality >22 weeks 2.7 to 5.3% and decrease in early neonatal mortality 3.3 to 0.8%.). We observed an increase in mortality, due to an increase in induced fetal mortality ≤22 weeks for neural tube defects, chromosomal anomalies, severe heart defects, and abdominal wall defects. Total perinatal mortality decreased (10.02 in 2004 to 6.37 per 1000 births in 2015). The decrease was mostly seen in fetal mortality >22 weeks (7.47 per 1000 births in 2004 to 4.62 in 2015), whereas decrease in neonatal mortality was less obvious (2.51 in 2004 to 1.57 per 1000 births in 2015). Perinatal mortality associated with CA dropped from 2.21 in 2004 to 1.89 per 1000 births in 2015.
Discussion and Conclusions: We observed an increase in mortality among fetuses and children affected with CA over the period 2001-2015, mainly due to an increase in induced fetal mortality ≤22 weeks gestation. Induced fetal mortality >22 weeks increased also, but to a lesser extent than fetal mortality ≤22 weeks. Early neonatal mortality among children born with CA decreased over the study period. As a result, the perinatal mortality among fetuses and children with CA remained relatively stable, but there was a shift within perinatal mortality from early neonatal to fetal mortality. The decrease in overall perinatal mortality rate (with or without CA) showed a decrease in the Northern provinces, whereas the perinatal mortality rate associated with CA remained stable. This implies that other actions that have been taken in

obstetric care to decrease the perinatal mortality may have impacted these findings.

Session III – Oral Communications

Surveillance Methods

Moderator: Mary Ann Thomas

An audit of antenatal detection rates in England for 12 specified fetal anomalies, 2016–2017
Sarah Stevens

Timeliness of data capture and processing in MACDP
Laura J Pabst

Challenges in implementing pulse oximetry screening for detecting congenital heart disease as part of birth defect screening in a middle- and low-income country setting
Nair Madhavankutty Sreehari

A novel software platform for assessing patterns of multiple congenital anomalies
AJ Agopian

The utility of routine hospital admission and mortality data to identify Spinal Muscular Atrophy Type 1 cases in England
Jeanette Aston

International Clearinghouse for Birth Defects
Surveillance and Research

AN AUDIT OF ANTENATAL DETECTION RATES IN ENGLAND FOR 12 SPECIFIED FETAL ANOMALIES, 2016-17

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ICBDSR Registry on which the work is based: National Congenital Anomaly and Rare Disease Registration Service (NCARDRS), UK

Background and Objectives: The National Health Service (NHS) offers all pregnant women in England a mid-pregnancy ultrasound scan for 11 structural fetal anomalies and biochemical screening for Down, Edwards and Patau syndromes through the Fetal Anomaly Screening Programme (FASP). Identifying false negative results poses a challenge to evaluating FASP performance, as subsequent diagnoses may be delayed, postnatal, or within a different setting. Having the necessary national data collection infrastructure, the National Congenital Anomaly and Rare Diseases Registration Service (NCARDRS) undertook an audit of FASP detection rates.

Methods: Data on pregnancies affected by any of the 12 fetal anomalies with an expected delivery date of 04/01/2016-03/31/2017 were linked from NHS trusts, laboratories, and other clinical services. Each anomaly was individually audited by NCARDRS and validated by the notifier. For quality assurance, data were only included from providers notifying the minimum expected number of anomalies given local characteristics. Condition-specific detection rates were calculated as the proportion of screened pregnancies and babies with confirmed fetal anomalies detected.

Results: Overall, 2,313 diagnosed anomalies were included from 71 screening providers, booking population 340,273 (47.4% of the national booking population). Ultrasound detection rates between 18+0 and 23+0 weeks gestation were anencephaly 91.7% (95%CI 64.6-98.5), bilateral renal agenesis 96.4% (82.3-99.4), congenital diaphragmatic hernia 67% (57.7-75.1), exomphalos 73.1% (53.9-86.3), cleft lip +/- palate 88.6% (84.4-91.8), lethal skeletal dysplasia 81.6% (66.6-90.8), serious cardiac 74.4% (70.4-78.1), spina bifida 96.2% (92.4-98.2), gastroschisis 87.5% (69-95.7), Patau syndrome 66.7% (43.7-83.7), and Edwards syndrome 69% (56.2-79.4). Down syndrome detection rates were combined test 82.1% (78.8-85.1) and quadruple test 66.3% (56.0-75.3).

Discussion and Conclusions: Detection rates between 18+0 and 23+0 weeks varied by condition. Most babies with anencephaly, gastroschisis, exomphalos, Patau syndrome, and Edwards syndrome were detected prior to the mid-pregnancy scan, and the inclusion of those detected using tests earlier in pregnancy markedly improved detection rates. The audit enabled FASP to better understand how many women learned about their babies' risks because of the national screening programme. This achievement demonstrates the value of a national register with the population coverage, case ascertainment, and expertise to link information which would otherwise exist in isolation. We expect data coverage and completeness to increase with annual repetition of the audit.

International Clearinghouse for Birth Defects
Surveillance and Research

TIMELINESS OF DATA CAPTURE AND PROCESSING IN MACDP

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ICBDSR Registry on which the work is based: Metropolitan Atlanta Congenital Defects Program (MACDP), GA, USA

Background and Objectives: National Birth Defects Prevention Network surveillance guidelines recommend data be 95% complete within two years of birth or fetal demise. Emerging risks to mothers and babies, including the Zika virus outbreak, demonstrate the need for rapid surveillance. The Metropolitan Atlanta Congenital Defects Program (MACDP) is a population-based birth defects surveillance system that collects information on birth defects that occur among residents of the central counties of Atlanta, Georgia. To ensure high data quality, MACDP employs active case finding in multiple facilities and implements comprehensive clinical and non-clinical reviews. This study aims to assess the feasibility of measuring timeliness of MACDP data.

Methods: Timeliness was initially measured by calculating days from the date of delivery to the date review processes were completed. Time to case completion was retrospectively calculated for all cases with a completion date in 2016. Data were stratified for cases that did/did not qualify for inclusion in the Birth Defects Study to Evaluate Pregnancy exposureS (BD-STEPS) case control study, as reviews are prioritized for these cases. Timeliness was also measured by calculating age at interview for BD-STEPS cases.

Results: Among 2016 cases, 97.7% were complete within two years from the delivery date. Average time from delivery to case completion was 12.5 months (range: 2.9-44.2 months). Timeliness did not differ between cases eligible for BD-STEPS (mean: 12.0 months; range: 2.9-33.0 months) and cases not eligible (mean: 12.5 months; range: 3.6-44.2 months). The average age at interview for BD-STEPS in 2016 was 8.1 months (range: 6.1-12.3 months).

Discussion and Conclusions: The difference between timeliness at age of interview and final completion for BD-STEPS cases highlights challenges in conceptualizing and measuring timeliness of birth defects surveillance data. Additional analyses are planned for 2017, stratified by defect type and number of abstractions. Data will also be stratified by prenatal vs. postnatal diagnosis. For postnatal diagnoses, days between date of diagnosis to the date review was completed will also be calculated. To more effectively respond to emerging threats to mothers and babies, MACDP is using these findings to identify additional meaningful timeliness measures for routine monitoring and improvement.

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CHALLENGES IN IMPLEMENTING PULSE OXIMETRY SCREENING FOR DETECTING CONGENITAL HEART DISEASE AS PART OF BIRTH DEFECT SCREENING IN A MIDDLE- AND LOW-INCOME COUNTRY SETTING

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ICBDSR Registry on which the work is based: Not Applicable

Background and Objectives: Kerala in India is one of the large state with 34 million population and best infant mortality rate (IMR) figures (10 per 1000 live birth based on 2017 data) is a progressive state, where various measures are taken for further reducing IMR. While considering the fixing of sustainable developmental goal targets, it was decided to focus on quality survival rather than survival. The platform included comprehensive newborn screening with components of visible birth defect screening, functional birth defect screening for congenital heart disease (CHD) using pulse oximetry (PO) and screening, and otoacoustic emissions for hearing screening. Metabolic screening for four parameters (TSH, CAH, G6PD, galactosemia) also were brought under a single umbrella. It was thought that such screening would be the most cost-effective way to improve quality survival of the newborn at this stage of development for any country. We now look back to evalute this program implemention.

Methods: Functional birth defects are a group of birth defects, which by screening during the early days of life, can improve survival of babies. CHD is among the most common functional birth defect, which is usually detected using PO. But the low specificity of PO screening as a tool for identifying CHD has already been discussed and evidence published. The effect of adding physical examination to the PO screening is also known. Thise presentation focuses on the problems that arose following implementation of a community-level program with 58 public sector delivery points in the state of Kerala, India, which is a low resource setting with quite good health indicators. Only 53% of the delivery points where birth defect screening was initiated were enrolled for PO screening due to resource constraints, but were able to include the delivery points with almost 70% of total deliveries per year.

Results: A protocol by American Academy of Pediatrics was used for the project and to interpret the results. It was observed that approximately 40% of cases were screened in the expected time interval of 24-48 hours. Screeners tended to complete the testing towards the end of 96 hours. Reasons observed for the delayed screening were reluctance of family members to come for screening and poor communication and very low efforts to disseminate the information among the public. A high incidence of false positives or test positives resulting in high resource utilization with regard to confirmation of diagnosis. This was due to poor adherence to the protocols for doing the screening, and improving adherence was able to bring the percentage failed from over 8% to 2.1% merely by training. It was also observed that adherence to the same screener also will improve the quality of screening. The knowledge level of the screener also produced an overall improvement in the test results.

Discussion and Conclusions: From our evaluation of this large scale public health intervention to reduced IMR, screening for CHD by PO screening was the most cost-effective tool. Screening over 80,000 newborns in the first few days of life, varying over a period of 12 to 96 hours, it was observed that beyond the use of PO screening, adherence to the screening protocol by continuous training, using the same screener, adding physical examination to identify clinical signs, such as a murmur, by using an electronic stethescope, decreasing the scope of manual error by automatic data capture, and defining a predictive score for ranking the physical examination findings will add to the value of PO screening for identifying CHD among newborns in a middle- and low-income country setting.

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A NOVEL SOFTWARE PLATFORM FOR ASSESSING PATTERNS OF MULTIPLE CONGENITAL ANOMALIES

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ICBDSR Registry on which the work is based: Texas Birth Defects Registry, USA

Background and Objectives: Clinical recognition of unique multiple congenital anomaly (MCA) patterns has been helpful for identifying and defining new syndromes, sequences, and associations. However, there are few examples where population-based data have been used to identify MCA patterns. We have developed a software platform providing large-scale assessment of combinations of congenital anomalies collected by birth defects surveillance programs.

Methods: To facilitate MCA assessment in large datasets, we developed an R-based software platform that will be made available to download for free. This platform can assess all possible 2-, 3-, 4-, and 5-way combinations for hundreds of congenital anomaly categories, outputting a metric based on the observed: expected prevalence ratio for each combination. An adjustment factor accounts for non-specific, generalized clustering of MCAs, which can lead to inflated estimates. To demonstrate proof-of-concept and feasibility, we applied our platform to data from the Texas Birth Defect Registry.

Results: When applied to data from a large congenital malformation surveillance program, our platform performed efficiently (e.g., analyzing 1.5 million 5-way combinations in less than a day). As expected, congenital anomalies that are known to be common among cases with nonsyndromic spina bifida had large adjusted observed to expected ratios, as did those known to be common among cases with trisomy 21. We estimate that computation of data from large birth defect surveillance programs will require less than a week.

Discussion and Conclusions: Our platform will allow for large-scale, systematic assessment of MCA patterns in large surveillance programs. This may help facilitate identification of new MCA patterns (e.g., associations) and/or better characterize known syndromes.

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THE UTILITY OF ROUTINE HOSPITAL ADMISSION AND MORTALITY DATA TO IDENTIFY SPINAL MUSCULAR ATROPHY TYPE 1 CASES IN ENGLAND

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ICBDSR Registry on which the work is based: National Congenital Anomaly and Rare Disease Registration Service (NCARDRS), UK

Background and Objectives: Collecting data on rare diseases is challenging, as data are scarce and often fragmented. The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) is evaluating the utility of routinely collected national data sources to support rare disease registration in England. In this study, we aimed to estimate population and birth prevalence for Spinal Muscular Atrophy Type 1 (SMA1) for England using Office for National Statistics (ONS) mortality data and national hospital admissions (HES) data.

Methods: We identified admissions in HES data with a finished consultant episode from April 01, 2008 to March 31, 2018 containing a diagnostic code of ICD-10 G12.0 Infantile spinal muscular atrophy, type I. We identified cases of SMA1 on the NCARDRS data management system. Vital status of patients was traced using the national Summary Care Record. Deaths from 2008-2016, with G12* Spinal muscular atrophy and related syndromes in the coded cause of death (COD) fields extracted from the mortality dataset. Free text COD fields were reviewed and deaths indicating either SMA1, SMA0, or SMA were identified. The resulting datasets were linked using the National Health Service (NHS) number.

Results: Using ONS mortality data and HES data, we identified 380 suspected SMA1 cases. We estimated a population prevalence of 1.9 per million (95% CI: 1.6-2.3) and a birth prevalence of 6.2 per 100,000 births (95% CI: 5.6-6.8). Of the 307 deaths in cases born in 2008-2016, 213 (69%) were ascertained from both HES and ONS mortality data; 14 (5%) from HES and 80 (26%) were from ONS mortality data only. One case was ascertained from NCARDRS only.

Discussion and Conclusions: We estimate that 1 in 16,150 babies born in England have SMA1 and that in mid-year 2016, there were 107 people living with SMA1 in England. Around one-quarter of deaths attributed to SMA1 in the mortality data had no code indicating SMA1 in the HES record in the time frame examined. These findings reinforce the need for a multi-source approach to case registration, including genetic diagnoses and subtyping. This will reduce case misclassification and improve the ascertainment usefulness of the data for healthcare planning and research.

Session IV – Oral Communications

Risk Factors

Moderator: Ieda M Orioli

Congenital malformations in children born to mothers with diabetes in the Czech Republic in the period 2000–2015
Antonin Šipek Jr

Recurrent Fetal Arthrogryposis: An Unexpected Diagnosis of Fetal Acetylcholine Receptor Inactivation Syndrome
Mary Ann Thomas

Hospital centered surveillance at birth 2011-2018 and assessment of environmental effectors of changes in reproductive health in Gaza, Palestine, reveals long-term impact of metals weapons-remnants
Paola Manduca

Major birth defects among offspring of Iowa Agricultural Health Study applicators
Paul A Romitti

Maternal MTHFR 677 CT/TT genotype is associated with increased risk of congenital heart defects in offspring
Yevheniya Sharhorodska

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CONGENITAL MALFORMATIONS IN CHILDREN BORN TO MOTHERS WITH DIABETES IN THE CZECH REPUBLIC IN THE PERIOD 2000 – 2015

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ICBDSR Registry on which the work is based: National Registry of Congenital Anomalies of the Czech Republic

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Background and Objectives: Diabetes mellitus (DM) in pregnancy is widely recognized as a risk factor for adverse prenatal development. The effect of DM in pregnancy on the prevalence of congenital anomalies has not been studied in our Registry. We present a retrospective epidemiological analysis of the prevalence of congenital anomalies in children born to mothers with DM compared to children born to mothers without DM.

Methods: We used data from the National Register of Reproductive Health at the Institute of Health Information and Statistics of the Czech Republic (IHIS CR) for the period 2000-2015. In our work, we divided all children born in the Czech Republic into two groups: children born to mothers with (any form of) diabetes mellitus in pregnancy and children born to mothers who did not have this disease. We also grouped children by those born with congenital anomalies (CA) and those born without CA.

Results: In the 16-year period (2000-2015), a total of 678,449 children were born in the Czech Republic, of which 52,123 children were born to mothers who were pregnant with DM. We also analyzed the representation of children born with CA in groups of mothers with DM and without DM. Prevalence of CA between the DM (3.97%) and non-DM (3.87%) groups was very similar and the difference was not statistically significant ($p = 0.236$). Another analysis compared the prevalence of a specific CA groups among diabetic and non-diabetic mothers among all children (with or without CA). Statistically significant differences were observed in Q20-Q28 and Q50-Q56 (higher incidence in DM mothers) and Q65-Q79 (lower incidence in DM mothers). We then analyzed the age of pregnant women. Diabetics in the whole set (regardless of CA) were on average 2 years older. This difference was statistically significant ($p < 0.001$).

Discussion and Conclusions: Our results did not show an overall increased risk of birth of a child with any CA in women with DM in pregnancy. However, we observed an increased risk for two specific groups of CA: congenital heart defects and congenital malformations of the genitals. For a group of pregnant women with DM in pregnancy, we further observed a statistically significant increase in age versus women without DM.

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RECURRENT FETAL ARTHROGRYPOSIS: AN UNEXPECTED DIAGNOSIS OF FETAL ACETYLCHOLINE RECEPTOR INACTIVATION SYNDROME

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ICBDSR Registry on which the work is based: Not applicable

Background and Objectives: Arthrogryposis encompasses a heterogeneous group of conditions with varying etiologies. Fetal acetylcholine receptor (AChR) inactivation syndrome is caused by maternal AChR antibodies crossing the placenta and inhibiting fetal AChR at the neuromuscular junction resulting in decreased or lack of fetal movement, thereby causing contractures. While this condition is well established in cases of maternal myasthenia gravis, it has only been described in pregnancies of three clinically unaffected mothers. We report a case and clinical details of recurrent fetal arthrogryposis mediated by maternal AChR antibodies in a woman with no clinical signs or symptoms of myasthenia gravis.
Methods: Investigations performed on the first fetus included chromosomal microarray, a 58-gene arthrogryposis panel, myotonic dystrophy gene testing, and fetal autopsy with neuropathology. Rapid aneuploid detection was conducted on the second fetus. After the first pregnancy, the ova donor was tested with a 94-gene myopathy panel. Antibody testing for the partner who carried the pregnancies included acetylcholine receptor, MuSK, and LRP4 antibodies.
Results: The investigations performed on the first fetus were unremarkable other than a heterozygous pathogenic variant in EXOSC3 detected by the arthrogryposis panel. This mutation is known to be associated with autosomal recessive pontocerebellar hypoplasia. However, fetal autopsy did not identify posterior fossa abnormalities on neuropathology. In addition, given the recurrence of arthrogryposis with a different sperm donor, this autosomal recessive condition was not considered the likely diagnosis. Autopsy did not identify mitochondrial anomalies nor loss of anterior horn cells in the spinal cord. Interestingly, the surrogate mother was found to be AChR antibody-positive with a titer of 6.1 nmol/L and was shown to have inefficiency in neuromuscular junction function on single fiber EMG despite having no clinical features of myasthenia gravis. Accordingly, the clinical diagnosis was fetal AChR inactivation syndrome.
Discussion and Conclusions: In contrast to cases of known maternal myasthenia gravis, fetal AChR inactivation syndrome is less commonly suspected when the mother is clinically asymptomatic. This case highlights maternal AChR antibody testing as an important investigation to consider in cases of undiagnosed fetal arthrogryposis, even if the mother does not show any signs or symptoms of myasthenia gravis. As this condition is mediated by maternal antibodies, there is a very high recurrence risk, possibly as high as 100%, in future pregnancies and there exists a potential for treatment in the form of IVIG.

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HOSPITAL CENTERED SURVEILLANCE AT BIRTH 2011-2018 AND ASSESSMENT OF ENVIRONMENTAL EFFECTORS OF CHANGES IN REPRODUCTIVE HEALTH IN GAZA, PALESTINE REVEALS LONG-TERM IMPACT OF METALS WEAPONS-REMNANTS.

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ICBDSR Registry on which the work is based: Not Applicable

Background and Objectives: In line with World Health Organization aims to assess health at birth and its environmental determinants, we conducted prospective longitudinal studies to obtain prevalence in 2011 and 2016-2018 of babies born preterm, with birth defects, and low birth weight at term in Gaza, Palestine and investigated the role of heavy metals in the environment in impacting these outcomes. Gaza was attacked militarily 3 times in the last 10 years with weaponry shown to discharge toxic and teratogenic heavy metals. Mothers directly exposed to these attacks had higher heavy metal load than those unexposed. The metals in contaminated mothers crossed the placenta. Investigation of changes in prevalence of adverse birth outcomes showed associations with maternal contamination with heavy metals and with metal distribution in time and over the territory. The role of confounders and genetic factors for this increased prevalence were ruled out.

Methods: Hospital based study in Shifa Maternity, Gaza included all women delivering in 2011 (n=4049), 2016 (n=6104), 2017 (n=2148), and 2018 (n=2900). EUROCAT questions were included in the questionnaire developed ad hoc by integrating 70 queries about specific local socioeconomic and physical environments (using data from the United Nations (UN) organization and local environmentalists). CD10 was used for diagnosis of major structural birth defects. The same methodology and procedures allowed for comparison of surveillance data. The load of 23 metals was determined by ICP/MS in the hair of mothers and newborns. Analysis for trend in changes in health across time was calculated using the chi-square test; logistic regression analysis identified predictor factors for negative outcomes. Comparison of metal loads with standards from outside the war area and between groups of women divided according to exposure or residence was conducted using Wilcoxon/Kruskal-Wallis tests; comparison of metal load across birth years was calculated using the median test.

Results: Prevalence of preterm birth and birth defects increased from 2011. No change in known co-factors of reproductive health justified this rise. Military attacks in 2012 and 2014 introduced a major novel risk for adverse outcomes at birth: contamination by teratogenic heavy metals weapon-remnants, which remain stable in the environment, accumulate in humans, and induce multiple epigenetic changes, was highest in women experiencing direct attacks. Delay in removal of rubble and weaponry and impaired rehabilitation of waste management increased the risks. Heavy metal load in women and babies were highest in 2016 for those living near unmanaged waste and predicted preterm birth and birth defects. Incidence of birth defects was steady in 2018, and the percentage of mothers housed in proximity to unmanaged waste was more than halved from 2017, due to partial reconstruction. The surveillance coupled with testing of heavy metal contamination show the role of these as inducers of negative birth outcomes.

Discussion and Conclusions: In Gaza, prevalence of birth defects grew steadily since Israeli withdrawl in 2005 and started attacks with weaponry containing heavy metals. Incidence of negative birth outcomes in 2011 was paralleled by higher contamination with weapons-remnant heavy metals among mothers

exposed to the attacks and their babies. Two years after the 2014 attacks, contamination by heavy metals and prevalence of birth defects and preterm birth were highest for residents near unmanaged waste, which became "hot spots" of metal contamination. No changes in prevalence were observed in 2018, when residences nearest to unmanned waste had greatly decreased. Our interpretation of the data is that heavy metals remnants of weapons are a major factor for the decrease in reproductive health in Gaza and for increased perinatal death, documented by UN Relief Works Agency. High loads of mercury and barium in newborns associated with maternal exposures and with birth defects or preterm births in 2011 and 2016. The role of other metals is also implied.

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MAJOR BIRTH DEFECTS AMONG OFFSPRING OF IOWA AGRICULTURAL HEALTH STUDY APPLICATORS

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ICBDSR Registry on which the work is based: Iowa Registry for Congenital and Inherited Disorders

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Background and Objectives: Studies of parental pesticide exposure continue to raise concerns about its potential teratogenicity; however, findings to date are equivocal, owed in part to several study limitations. To address these limitations, we investigated major birth defects among offspring of Iowans enrolled in the United States Agricultural Health Study (AHS), a prospective study of chronic disease among pesticide applicators and their spouses.

Methods: We linked applicator and spouse data from the AHS with Iowa birth data (1972-2014) and identified 42,460 liveborn offspring, including 24,256 born from 1983-2010. Data for these 24,256 offspring were linked with surveillance data from the Iowa Registry for Congenital and Inherited Disorders. We investigated relations between paternal application of 121 pesticides shortly before or during the index pregnancy and 9 birth defect groups in offspring. Associations were estimated for defect groups with ≥5 exposed offspring compared to offspring of unexposed applicators per pesticide, adjusting for relevant covariables.

Results: We identified 400 (1.6%) of the 24,256 offspring to have a major birth defect, with heart, genitourinary, gastrointestinal, and musculoskeletal defects most frequently observed. Overall, 32 of the 121 pesticides had ≥5 exposed offspring in a case group, producing 128 estimated associations. We observed positive associations (adjusted odds ratios 1.5-3.0) for 34 pesticide-case group combinations. Eight pesticides produced positive associations in two or more case groups and included: S-Ethyl-Dipropylthiocarbamate (craniofacial, gastrointestinal); petroleum oil/distillates (craniofacial, gastrointestinal, musculoskeletal); pendimethalin (craniofacial, musculoskeletal); permethrin (craniofacial, genitourinary, heart, musculoskeletal); terbufos (craniofacial, musculoskeletal); carbofuran (craniofacial, genitourinary, musculoskeletal); carbaryl (craniofacial, musculoskeletal); and coumaphos (genitourinary, musculoskeletal).

Discussion and Conclusions: Although limited to liveborns, our findings from this large cohort suggest that paternal application of several pesticides shortly before or during early pregnancy contributed to an increased risk of major birth defects, particularly craniofacial, musculoskeletal, and genitourinary defects. Future work will investigate major birth defects among pregnancy losses and terminations.

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MATERNAL MTHFR 677 CT/TT GENOTYPE IS ASSOCIATED WITH INCREASED RISK OF CONGENITAL HEART DEFECTS IN OFFSPRING

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ICBDSR Registry on which the work is based: Not Applicable

Background and Objectives: Congenital heart defects (CHD) are among the most common congenital anomalies worldwide, occurring in approximately one in one-hundred living newborns. Heart defects at birth occur as an isolated malformation, but are also associated with other anomalies or occur as part of a syndrome. The etiology of CHD is only partly illuminated, but most CHD are thought to be of complex multifactorial origin, with one or more alleles at a number of loci interacting with environmental factors. Maternal multivitamin supplementation containing folic acid reduces the risk of neural tube defects, and evidence suggests that it may be associated with other reproductive outcomes, including CHD. Our previous results revealed in pregnant women with prenatally diagnosed CHD, an association of particular alleles of genes important in folic acid metabolism.

Methods: The purpose of our study was to establish the frequency of common single nucleotide polymorphisms in the MTHFR and MTHFD1 genes among women from West Ukraine in cases of prenatally diagnosed CHD and replication of the obtained results using a larger number of cases. Genotyping of MTHFR 677C>T (rs1801133), MTHFR 1298 A>C (rs1801131), and MTHFD1 1958G>A (rs2236225) polymorphisms was performed in 67 women with prenatally diagnosed CHD in the fetus and in 62 healthy women. The molecular- genetic analysis was performed by Polymerase Chain Reaction and Restriction Fragment Length Polymorphism analysis. Statistical analysis was conducted by chi-square tests and odds ratio (OR) estimation.

Results: We did not observe any significant differences in the MTHFD1 1958G>A (rs2236225) genotype and alleles frequencies between case and control mothers ($p>0.05$). The frequency of MTHFR 677CC genotype was significantly more often in control compared with case mothers (51% and 32%; $p=0.04$) and was associated with a two-fold decreased risk in delivering offspring with CHD [OR=0.46 (95% CI: 0.22 - 0.96)]. The genotypes MTHFR 677CT or MTHFR 677TT were associated with two-fold increased risk in delivering offspring with CHD [OR=2.17 (95% CI: 1.04 – 4.51)]. In cases of MTHFR 1298 A>C and MTHFD1 1958G>A polymorphisms, the frequencies of alleles and genotypes were not significantly different in women with prenatally diagnosed CHD in the fetus compared to controls ($p>0.05$).

Discussion and Conclusions: Maternal MTHFR 677 CT/TT genotype seems to be highly probable risk factor for Ukrainian women to have a child with CHD, whereas the MTHFR 677CC genotype provides a credible protective effect. Studies on the relation between MTHFR 677CT polymorphism and congenital anomalies mainly focused on neural tube defects, a neural crest derivate. In our study, the maternal MTHFR 677CT and TT genotypes appeared to be genetic risk factors, in particular, for CHD in offspring. This observation supports the hypothesis that impaired folate metabolism interferes with the developing heart, possibly by affecting neural crest cells. Our results suggest a possible protective effect of periconceptional folic acid supplementation. It is extremely important that supplementation be performed in countries where food fortification with folic acid is not yet the norm.