08.00 - 08.30  Registration in front of the Congress Hall
08.30 - 08.45  Opening ceremony
Session 1: 50 years after thalidomide therapy
Chairs: Helen Dolk and Lorentz M Irgens
08.45 - 09.05  50 years on from thalidomide
Patricia Boyd
09.05 - 09.25  Thalidomide: what we have learned 50 years after the tragedy
Eva Bermejo Sanchez and Maria Luisa Martinez-Frias
09.25 - 09.30  Discussion
Session 2: Public health policies
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09.30 - 09.50  EUCERD and the EUCERD Joint Action: working for rare diseases
Stephen Lynn and Kate Bushby
09.50 - 10.00  Enabling public health action for congenital anomalies in low- and
middle-income countries
Sagoo Gurdeep, Luis Nacul, Alison Stewart, Corinna Alberg,
Susmita Chowdhury, Matthew Darlison, Christopher Grollman,
Alison Hall, Bernadette Modell, Sowmiya Moorthie, Mark Kroese
and Hilary Burton
10.00 - 10.20  Register of congenital heart disease in Croatia
Ivan Malčić and Daniel Dilber
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10.30 - 11.00  Coffee break and Poster session
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11.00 - 11.10  The role of stress in early pregnancy in the aetiology of gastroschisis
Stephen Palmer, Annette Evans, Shantini Paranjothy, Simon
Huddard, Mark Drayton, Helen Broughton, Judith Rankin, Elizabeth
Draper and Alan Cameron
11.10 - 11.20  Riscripro-Sentieri project: surveillance of adverse reproductive
outcomes in Italian polluted sites
Fabrizio Bianchi, Gianni Astolfi, Pietro Carbone, Maurizio Clementi,
Susanna Conti, Ivano Iavarone, Paolo Ricci, Gioacchino Scarano,
Gabriella Dardanoni, Giovanna Tagliabue, Michele Santoro,
Federica Pieroni and Anna Pierini
11.20 - 11.30  Traffic-related air pollution and risk of congenital anomalies in Barcelona
Anna Schembari, Mark J Nieuwenhuijsen, Joaquin Salvador, Audrey de Nazelle, Marta Cirach, Payam Dadvand, Gerard Hoek, Rob Beelen, Xavier Basagaña, and Martine Vrijheid
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Chairs: Eliza Canzolari and Ingeborg Barisic

11.30 - 11.50  Advances in genetic testing for children with congenital anomalies and developmental disorders
Dian Donnai

11.50 - 12.10  Twinning and congenital anomalies
Albert Schinzel

12.10 - 12.20  The impact of consanguinity on birth defects in a Saudi population: a case/control study
Muhammad Ali Majeed-Saidan, Amar Nassar Ammari, Amal Al Hashem, Maha Al Rakaf, Mohammed Shoukri, Mohammad Tariq, Ester Game and Ahmed Kurdi

12.20 - 12.30  Noonan Spectrum test – one year on…
Silvia Borras, Sarah Spiden, Ann Curtis, Karen Livermore, Dayne Bromley, Emily Stephenson, John Short, Sandra Moore and Rohan Taylor

12.30 - 12.45  Discussion

12.45 - 14.00  Lunch and Poster Session

Session 5: Medication in pregnancy
Chairs: Hermien de Walle and Ester Garne

14.00 - 14.20  Different study designs for signal detection and signal evaluation to identify teratogenic risks of medicines used in pregnancy
Lolkje TW de Jong-van den Berg

14.20 - 14.40  Trends in medicine use during pregnancy in Finland 1996-2010
Anna-Maria Lahesmaa-Korpinen, Annukka Ritvanen, Miia Artama, Mika Gissler, Heli Malm, Marja-Leena Nurminen and Leena Saastamoinen

14.40 - 14.50  An evaluation of e-pharmacies selling the teratogenic drug, Isotretinoin
Briege M. Lagan, Helen Dok, White Bronagh and M. Sinclair

14.50 - 15.00  Living with Fetal Valproate Syndrome: experiences of seven young people
Emma Douglas, Diana Scotcher, Rhona Macleod, Rebecca Bromley and Jill Clayton-Smith
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Breidge Boyle, Helen Dolk, Joan Morris, Roy McConkey and The EUROCAT Working Group |
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| 16.10 - 16.20 | Closing remarks and Poster prize                                      |
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- CONGENITAL MALFORMATIONS AND PERINATAL MORTALITY AT GENERAL COUNTY HOSPITAL VINKOVIĆI, CROATIA 1974-2012, M. Jurković and D. Švagelj
- CONGENITAL HEART DISEASE IN CHILDREN WITH DOWN’S SYNDROME, V. Mahulja-Stamenković, R. Krajina, I. Bilić Čače, N. Čače and B. Peter
- POPULATION-BASED CONGENITAL ANOMALIES REGISTRY: VALIDITY OF HOSPITAL DISCHARGE RECORDS AS INFORMATION SOURCE FOR CASE IDENTIFICATION, C. Martos, C. Cavero, S. Gimeno, R. Guaita, L. Páramo, C. Barona, and O. Zurriaga
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12th European Symposium on Congenital Anomalies

June 14th 2013
Zagreb, Croatia

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L1
50 YEARS ON FROM THALIDOMIDE

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The first warning of the teratogenic effect of thalidomide came in 1961 but affected babies continued to be born until 1963. A direct result was more pertinent testing of new drugs. Many case reports raised the possibility of new teratogens and increasing use of epidemiological studies assessed the complicated issue of environmental causes. In the subsequent 50 years there has been an explosion of new knowledge around birth defects. From the point of view of public health, thalidomide and the proportional increased contribution of birth defects to infant mortality, led to surveillance programmes such as EUROCAT being set up and research being carried out to assess aetiology. Important new teratogens (e.g. antiepileptics, alcohol) have been identified; the importance of primary prevention (e.g. neural tube defects/folate, rubella vaccination); the emergence of prenatal diagnosis, screening and legalisation of termination of pregnancy have had huge though varying impacts. New knowledge in genetics has led to the understanding and identification of more specific chromosome and single gene defects. Assisted reproductive technology and associations with rare birth defects have raised questions relating to cause. The above are just a few examples of new knowledge acquired over the last 50 years. Although research into aetiology is impressive, the fact remains that the cause of most birth defects remains unknown. With the new knowledge around primary prevention e.g. folate supplementation, why is implementation of such knowledge so variable? To detect another thalidomide disaster quickly linkage of prescription and surveillance data is needed, yet this is still done only by a small minority. With all the exciting new developments in molecular genetics, the hopes that knowledge of mechanisms would lead to cures and to non-invasive prenatal diagnosis are yet to be fully realised. The importance of population based data for surveillance and monitoring trends remains the absolute requirement.
In 1954, thalidomide was synthesized for the first time. In 1957, it was marketed in Europe for diverse indications, including anxiety, insomnia, nausea and vomiting in pregnant women. It reached rapidly the five continents. In 1961, Dr. W. Lenz, from Germany, reported on a relationship between limb reduction defects and prenatal exposure to thalidomide. This relationship was published in The Lancet in 1962 and it resulted in withdrawal of the drug from the market. Nevertheless, at least 5,850 cases were affected after clear evidence of exposure. The most striking defects caused by thalidomide are limb reduction defects (particularly amelia and phocomelia), but it also caused other limb anomalies, as well as severe ear defects, including anotia, eye anomalies, and defects affecting other organs and systems. All of them composed the so-called thalidomide embryopathy. Etiological evaluation of supposedly affected patients has been very difficult, since there is no specificity for the defects caused by thalidomide, as it occurs with other teratogens. Moreover, there are different syndromes, which are clinically indistinguishable from thalidomide embryopathy. Today, mainly, we have learnt the following: the sensible period comprises days 35-49 from the last menstrual period; the risk of being affected after exposure in this period is 50%; there is no specific teratogenic effect of the exposure; even in those exposed in that period, their defects can be due to other causes; population risk must be considered in any assessment. This awful experience led to the conclusion that the placenta does not protect the embryo/fetus as previously thought. It also raised the need of registry systems of newborn infants with congenital anomalies that could allow an early detection of the possible increases in the frequency of some or several birth defects if a teratogen has been introduced in a specific location. Facing the impossibility of performing teratology studies in humans, it was clear that epidemiological research on congenital anomalies was essential and that accurate records of exposures during pregnancy had to be added to the registry of infants with these conditions. Meantime, strict regulations for drug marketing and categorization of drugs according to their potential developmental effects were progressively adopted in different countries. It is a fact that many children worldwide (adults today) suffered terrible consequences of the prenatal exposure to this teratogen. Undoubtedly, their experience has also served to prevent many infants to be affected by similar circumstances, since many preventive measures have been developed.
EUCERD AND THE EUCERD JOINT ACTION: WORKING FOR RARE DISEASES

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The EUCERD (European Union Committee of Experts on Rare Diseases) is mandated to assist the European Commission in formulating and implementing the Community’s activities in the field of rare diseases, to foster exchanges of relevant experience, policies and practices between the Member States and stakeholders. Rare diseases are a priority area for action in the current Public Health Programme (2008-2013). These activities have been defined in the Communication of the European Commission, entitled “Rare Diseases: Europe’s challenge” (published 11 November 2008) and the Council Recommendation on an action in the field of rare diseases (published 8 June 2009). The EUCERD Joint Action: Working for Rare Diseases, started on 1 March 2012 and supports the activities and mandate of the EUCERD Committee.

The Joint Action comprises five main areas of work:

- Support for the implementation of plans and strategies for rare diseases at national level,
- Promoting the standardisation of rare disease nomenclature at international level,
- Mapping the provision of specialised social services and integration of rare diseases into mainstream social policies and services,
- Leveraging of the value of EU networking for improving the quality of care for rare diseases,
- Promoting the integration of RD initiatives across thematic areas and across Member States.

The expected outcome of the Joint Action is an integrated strategy for the implementation of rare disease policies through the exchange of experience between Member State health authorities already involved in rare disease policy definition and implementation and via a series of recommendations from the EUCERD and clear communication of these recommendations to national policy makers, patient organisations and learned societies.
L4
REGISTER OF CONGENITAL HEART DISEASE IN CROATIA

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Objective: We established the Register to study the distribution of congenital heart diseases (CHD) in Croatia, risk factors and outcome analysis.

Methods: All children born between October 2002 and October 2007 in Croatia, with the diagnosis of congenital heart defect were collected in the Register set up according to the EUROCAT principles. After 2007, we joined EACTS congenital cardiac surgery database and continued with outcome analysis of children having undergone cardiac surgery to the present.

Results: Between October 1, 2002 and October 1, 2007, there were 205,051 live births in Croatia, of which 1,480 patients were diagnosed with CHD, accounting for 0.72% of the live-born children. The most common diagnosis was ventricular septal defect with a percentage of 34.6%; 14.5% of all patients had associated non-cardiac anomalies. Of these, 50.2% had chromosomal defects, 14.4% syndromes and 35.3% other major congenital anomalies; 7.16% of children were born to mothers with acute febrile illness during pregnancy, 3% to mothers with chronic disease, 4.1% of children had CHD in family history, and 3.7% had other hereditary diseases in family history. Most of the children with CHD needed follow up only, 18.5% needed medications, 1.5% catheterization as treatment procedure, and 29% one or more operations. During the last four years of the study, the number of operations performed in Croatia showed linear increase: 55, 78, 121 and 126 operations were performed in 2008, 2009, 2010 and 2011, respectively. Early mortality was 1.82%, 5.41%, 3.64% and 3.48% in 2008, 2009, 2010 and 2011, respectively. The increase in the number of operations was followed by a satisfactorily low mean mortality rate of 3.85%. The most complex operations are still performed in foreign centers.

Conclusion: The importance of registries lies in the field of epidemiologic research, but they can also prove useful for evaluation of medical care and quality of treatment.
The birth of a child with congenital anomalies, or the diagnosis of developmental delay, provokes much distress for the family and triggers many questions such as 'what caused the problem', 'what does it mean for my child' and 'will it happen again'? None of these questions can be answered without a precise diagnosis. Over the years, many new syndromic entities have been delineated but, until around 20 years ago, diagnosis rested mainly on clinical pattern recognition with a few being diagnosed by traditional chromosomal analysis and even fewer by specific gene tests. In the absence of a diagnostic test, genetic counselling rested on experience of a few families in the literature and prenatal diagnosis was not possible other than ultrasound scanning. The options for families with a child with an unknown pattern of anomalies were even more limited. However over the last 20 years many new diagnostic methods have been introduced; firstly these were targeted investigations such as fluorescent in situ hybridisation (FISH) or individual gene tests where clinical suspicion of a specific syndrome was investigated. Then the tests began to be more general such as tests for deletions of subtelomeric regions applicable to patients with any unknown pattern. More recently there have been major advances in testing children with patterns of malformations. Many laboratories have ceased routine karyotyping for testing children postnatally and have moved to first line microarray testing with a much greater diagnostic rate. Whilst there have been great benefits in terms of diagnostic yield and delineation of many new recurrent pattern syndromes, we are still learning how best to interpret some of the findings. Interpretation is also a big issue for Next Generation Sequencing technologies which are increasingly being translated from research to diagnostic service applications. Exome sequencing or sequencing of large panels of genes for broad applications are now offered from many centres with the promise of whole genome sequencing before too long. Expertise in bioinformatic analysis is crucial and there are also ethical issues which require consideration. The underlying basis of single malformations is still poorly understood unless they are clearly inherited
such as some types of cleft lip+/− palate and there are still many cases of multiple malformations that defy diagnosis. Recent research has found causative mutations in some puzzling disorders such as Proteus syndrome but in a mosaic state, which was why investigations of DNA from blood did not reveal anything. For unknown cases large scale initiatives such as the DDD study in the UK (Deciphering Developmental Disorders www.ddduk.org) may offer solutions by linking genotypes with phenotypes from many thousands of cases.
Congenital developmental defects (CDD) are 2.5 times more frequent in twins as compared to singletons. This increase is almost entirely due to a higher incidence in monozygotic twins and holds true also for higher-order twins (triplets, quadruplets, etc.). If CDD are subdivided into malformations, deformations, disruptions, monogenic disorders, chromosome aberrations, polygenic disorders and those of completely unknown etiology and pathogenesis, it turns out that, while their incidence in twins is not increased in monogenic disorders and chromosome aberrations, the overall increase is mainly due to malformations, deformations and disruptions. Deformations are defined as secondary alterations, due to pressure, of structures that initially were correctly formed. It is evident that the lack of space in twin pregnancies is the main reason for the latter, and consequently their increased incidence is not confined to monozygotic twins. Vascular disruptions, however, occur with an increased incidence in monozygotic twins with a single placenta. Their pathogenesis is based on vascular collaterals between the two segments of such placentas, followed by early prenatal demise of one of the partners. Postmortem blood coagulation and/or tissue necrosis may be followed by embolization of arteries in the surviving twin following transmission of a thrombus to the vascular net of the co-twin. Mostly, cerebral arteries are involved, and the consequences are necrosis of brain tissue, porencephalic cysts, and the clinical picture of severe brain dysfunction combined with spastic paraplegia. The second most frequent manifestation, and most often combined with the former, is intestinal obstruction as the consequence of embolization of a branch of the mesenteric artery. Since it may happen that a deceased twin is resorbed or remains undetected (e.g., as fetus papyraceus), such events might be more frequent than detected among newborns: the twinning rate at 12 weeks of gestation is assumed to be twice as high as in newborns. The highest contribution to the increased incidence of CDD in twins constitute malformations of early embryonic origin. Malformations (concerning single organs or structures) and malformation complexes (concerning primary and secondary structures) are, in contrast to deformations and disruptions, primarily incorrectly formed structures. Thus, most malformations of inner organs, e.g., the heart, brain and kidneys, fall into this category. A closer look to malformations in twins shows that the earlier a malformation is formed and the later twin separation occurs, the higher is its incidence in twins. The highest incidence is found in extrophy of the cloaca, sirenomelia, the VATER association and sacro-coccygeal
teratoma (the latter is in fact an undifferentiated conjoint twin) and in conjoined and monochorionic monoamniotic twins. Twin partners of a severely disorganized twins (acardius, acephalus etc.) are, if they feature a CDD, always concordant for the malformation in the former. Apart from this, concordance of such malformations is rare and almost never complete to the extent of a defect. In first trimester spontaneous abortions, the incidence of twins is at least twice as high as in full-term newborns, the preponderance of monozygotic over dizygotic twins is by far higher, and concordance for the malformation(s) is also much higher, which explains the early demise. Recent studies using molecular markers have shown that in twins with one partner affected with a CDD and the other normal, there is more discordance for genomic variants than in controls. These findings indicate that an early accident, be it genetic or environmental, may cause both twin separation and a CDD in one or both of the partners. Concordance versus discordance for such a CDD seem not to be valid criteria for genetic versus non-genetic origin of these defects. Monozygotic twinning per se can be considered a defect in humans, thankfully often with favorable outcome.
Since the thalidomide disaster regulations for reproductive toxicity, tests have become mandatory and birth defect registries have been set up. Medicine use in pregnancy can be related to a wide range of adverse effects, including not only congenital malformations but also preterm birth, intrauterine growth retardation, spontaneous abortion, late fetal and neonatal death or developmental disabilities. Ideally one would identify the teratogenic potential of medicines before they are used in humans. However, information on reproductive toxicity is only available from pre-marketing animal studies, which are seriously limited to predict human teratogenicity. Moreover, pregnant women are excluded from pre-marketing clinical trials in humans. Another complication is that teratogenicity is often not related to the class of drug or what is known about its pharmacology or toxicology. Therefore, we learn about teratogenic effects in humans only post-marketing when a drug has been used in pregnant women. In the post-marketing setting, three main approaches are used to identify teratogenic risks possibly associated with medicine use in pregnancy: spontaneous adverse event reports, cohort studies and case-control studies. Spontaneous reports can provide a signal of an increased risk and this method is most suitable for signal detection of very high risks of a specific malformation, to be followed up by evaluation in cohorts and case-control studies. Cohort studies follow prospectively women exposed to a specific drug, determine the outcome and compare the frequency with the outcome among unexposed pregnancies. Cohort studies provide an opportunity to evaluate a range of pregnancy outcomes associated with exposure. Cohort studies are suitable to detect high teratogens, or to generate signals. In case-control studies, cases of a specific malformation are selected and compared with controls with reference to the exposure of interest. Case-control studies are mainly used to evaluate signals. However, all methods are hampered by the fact that for this type of evaluation drugs cannot be grouped pharmacologically (each drug need to be evaluated separately) and many of the outcomes of interest are rare and they cannot be grouped either. As a consequence, the population base needed for any evaluation is substantial. This presentation will illustrate the value of the different study designs and their contribution to risk assessment in pregnancy during the lifetime of a drug with historical and recent studies.
Preimplantation genetic diagnosis (PGD) has started at the University Medical Center Ljubljana in 2004. A total of 81 patients underwent 147 PGD cycles. The most frequent indications were monogenic diseases (39%), followed by chromosome translocations (35%), preimplantation genetic screening (19%) and X-linked diseases (7%). Among monogenic disorders, the most frequent disorders were Huntington disease, myotonic dystrophy, Duchenne muscular dystrophy/Becker muscular dystrophy and spinal muscular atrophy. Embryo transfer was possible in 102 PGD cycles and resulted in 32 clinical pregnancies. The clinical pregnancy rate was 22% per cycle and 31% per embryo transfer. Sixteen unaffected children were born and five pregnancies are ongoing. Ten (31%) pregnancies ended in spontaneous miscarriage. Reduction of the abortion rate appears to be promised by the recently introduced array comparative genomic hybridization approach, which enables screening for all 24 chromosomes as well as for significant genomic rearrangements. Future application of the next generation screening approach in PGD provides a potential for general genetic screening and improved prevention of genetic disorders, but also rises several professional and ethical problems and dilemmas.
SESSION 2: PUBLIC HEALTH POLICIES

S1 ENABLING PUBLIC HEALTH ACTION FOR CONGENITAL ANOMALIES IN LOW- AND MIDDLE-INCOME COUNTRIES

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Many low- and middle-income countries are achieving significant reductions in infant and child mortality. A greater proportion of the remaining burden is due to congenital anomalies. The importance of tackling these conditions is highlighted by both the need to achieve MDG 4 and a call for action by the World Health Assembly (WHA) in 2010. Due to the importance of congenital anomalies as a public health problem, we produced a web-accessible ‘Toolkit’ delivering a step-wise guide, based on the principles of health needs assessment as a prerequisite for strategic planning to develop regional and national programmes to tackle congenital anomalies. This addresses the need highlighted by the WHA resolution that “international technical guidance will be required to help ministries with organized assessment of requirements and costs and with support in choosing priorities”. The Toolkit (http://toolkit.phgfoundation.org) was prepared by a multi-disciplinary team with advice from external experts. These documents provide background information on key concepts as well as specific tools that allow assessment of need in relation to particular topics. The Toolkit contains 12 clinical topics (e.g. NTDs) included on the basis of their impact on public health worldwide, and five service topics (e.g. newborn screening). The Toolkit was designed for use by people unfamiliar with public health methods and enables users to develop or reformulate policies, programmes and services to reduce disease burden. It guides users through a systematic, multi-stage process providing access to international data and a roadmap to assessing health needs. An important strength of the Toolkit is its flexibility. Not all users may need, or have the resources, to carry out a detailed assessment for a particular topic and can choose to collate data on disease burden or concentrate on qualitative evaluation of existing services.
S2
THE ROLE OF STRESS IN EARLY PREGNANCY IN THE AETIOLOGY OF GASTROCHISIS

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Background: The incidence of gastroschisis, a congenital anomaly where the infant abdominal wall is defective and intestines protrude from the abdominal cavity, is increasing in many countries. The role of maternal stress in some adverse birth outcomes is now well established. In a case-control study in the United Kingdom we tested the hypothesis that major maternal stressful life events in the first trimester are risk factors for gastroschisis, and that social support is protective.

Methods: Gastroschisis cases and three controls per case (matched for maternal age) were identified at routine 18-20 week fetal anomaly ultrasound scan, in 2007-2010. Face to face questionnaire interviews were carried out during the antenatal period (median 24 weeks gestation) asking about serious stressful events and social support in the first trimester. Data were analysed using conditional logistic regression.

Results: Two or more stressful life events in the first trimester (adjusted OR 4.9; 95% CI 1.2-19.4), and moving address in the first trimester (aOR 4.9; 95% CI 1.7-13.9) were strongly associated with increased risk of gastroschisis, independent of behavioural risk factors including smoking, alcohol, and poor diet. Perceived availability of social support was not associated with reduced risk of gastroschisis (aOR 0.8; 95% CI 0.2-3.1).

Conclusion: Stressful maternal life events in the first trimester of pregnancy including change of address were strongly associated with a substantial increase in the risk of gastroschisis, independent of stress related high risk behaviours such as smoking, alcohol consumption and poor diet. This suggests that stress pathways are involved in the aetiology of gastroschisis in a case-control study in the United Kingdom.
RISCRIPRO-SENTIERI PROJECT: SURVEILLANCE OF ADVERSE REPRODUCTIVE OUTCOMES IN ITALIAN POLLUTED SITES

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SENTIERI project is the first mortality study among residents in 44 Italian polluted sites of national interest (IPSs). Other than the mortality study, the reproductive health issue has been recognized as a topic to investigate in polluted areas, as well as to answer communities concern and support decision-makers. In 2012, the RISCRIPRO-SENTIERI project was launched by the Italian Ministry of Health to investigate adverse reproductive outcomes (AROs) in the sites covered by congenital anomalies (CAs) registries. As background, some notions have been considered: an environmental factor can play a role either as mutagen in preconception exposure or as teratogen in postconception exposure; the relatively short latency from exposure to outcome; the high sensitivity of the developing fetus; AROs may serve as sentinels for estimating environmental risks in polluted areas. The choice of CAs to be included in the study has been based on the results completed for SENTIERI. Data on CAs are produced by seven registers included in the Italian CA Registers Committee. Registers are active in 16 out of 44 IPSs included in SENTIERI, covering 119 municipalities. Environmental exposure in IPS includes chemical substance plant, petrochemical plant/refinery, steel industry, electric power plant, mine/quarry, harbor area, asbestos/other mineral fibers, landfill, and incinerator. Other exposures include air pollution, smoking, drinking, occupational exposure, and socioeconomic status. The main EUROCAT groups/specifc anomalies will be included. In each IPS, the expected cases for each CA will be estimated using the registry birth prevalence. The study periods will be chosen according to data available from the registers for the 1996-2010 period. In such a period, approximately 600,000 births were surveyed in the IPSs areas covered by the CA registries. Risk excesses ranging from 1.2 to 2.0 can be detected according to the occurrence of CA and the type of IPSs examined. Other AROs (low birth weight, prematurity, sex ratio) will be evaluated by the Hospital Discharge Records and Birth Medical Records available at the national level. The results will be used to provide recommendations for public health intervention and research priorities in the environment-health setting.
TRAFFIC-RELATED AIR POLLUTION AND RISK OF CONGENITAL ANOMALIES IN BARCELONA

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Background: A recent meta-analysis suggested evidence for an effect of ambient air pollutants on the risk of certain congenital heart defects. However, few studies investigated the effects of traffic-related air pollutants with sufficient spatial accuracy.

Objectives: To evaluate the risk of congenital anomalies associated to traffic-related air pollution exposure, estimated by temporally adjusted spatial exposure models in Barcelona.

Method: Non-chromosomal cases (n=2,247) and controls (n=2,991) were selected from the population-based Barcelona congenital anomaly register between 1994 and 2006. Land use regression models developed for the ESCAPE project were applied to residential addresses at birth to estimate spatial exposure to nitrogen oxides and dioxide (NO, and NO2), particulate matter with diameter ≤10 μm (PM10), between 10 μm and 2.5 μm (PMcoarse) and ≤2.5 μm (PM2.5) and PM2.5 absorbance. Spatial estimates were adjusted for temporal trends using data from routine monitoring stations for weeks 3 to 8 of each pregnancy. Logistic regression models were used to calculate odds ratios for 18 congenital anomaly groups associated with an interquartile range increase in spatial and spatiotemporal exposure estimates.

Results: In spatial and spatiotemporal exposure models, we found associations between coarctation of the aorta and NO2 (adj.OR spatio-temporal =1.15; 95%CI 1.01-1.31), digestive system defects and NO2 (adj.OR spatio-temporal =1.11; 95%CI 1.00-1.23), and abdominal wall defects and PMcoarse (adj.OR spatio-temporal =1.93; 95%CI 1.37-2.73). Other statistically significant OR were found in the spatial model only or in the spatiotemporal model only, but not in both.

Conclusions: Overall, our results do not indicate an association between traffic-related air pollution and most groups of congenital anomalies. Findings for coarctation of the aorta are consistent with the previous meta-analysis. The increased risks of digestive system anomalies and abdominal wall defects are novel and call for confirmation.
THE IMPACT OF CONSANGUINITY ON BIRTH DEFECTS IN A SAUDI POPULATION: A CASE/CONTROL STUDY

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The role of consanguinity on birth defects outside the chromosomal and inherited disorders has always been debatable. The aim of the study was to assess the independent role of consanguinity on birth defects in a population with a high rate of consanguineous marriage. This case-control study nested within a 3-year cohort study of fetal and neonatal malformations in a Saudi population was conducted at Prince Sultan Military Medical City, Riyadh Region, Saudi Arabia. During the first two years of the study, there were 19,165 births: 785 babies with birth defects and 745 babies selected as controls. The prevalence rate of birth defects was 41/1,000 births. The malformations were classified according to the Eurocat flowchart. Consanguinity had a statistically significant contribution in cases of genetic syndrome, isolated renal defect and other isolated malformations ($P<0.05$). It had no statistically significant contribution in cases of chromosomal aberration, neural tube defect, isolated congenital heart disease, and multiple malformations. The $P$ value of the effect of consanguinity on various malformations will be presented at the meeting. The multivariant logistic regression analysis showed that consanguinity is an independent risk factor for this high rate of birth defects in the study population ($P=0.0002$). The following conclusions were drawn: the prevalence rate of birth defects in the study population is higher than that reported from European countries; and consanguinity has an independent role in the high rate of birth defects.
Germline mutations in genes encoding protein components of the Ras/MAPK signal transduction pathway are the cause of a spectrum of autosomal dominant disorders: Noonan syndrome, Cardio-facio-cutaneous syndrome (CFC), Costello syndrome, Noonan syndrome with multiple lentigines (formerly known as LEOPARD syndrome), Legius syndrome, Noonan-like syndrome with or without juvenile myelomonocytic leukaemia and Noonan-like syndrome with loose anagen hair. The pathway plays a critical role in control of proliferation and differentiation of multiple cell types; therefore its deregulation gives rise to profound developmental consequences. These include facial dysmorphism, a wide spectrum of cardiac disease, postnatal reduced growth, ectodermal and skeletal defects, haematological malignancies and variable cognitive deficits. With incidence ranging from a few hundred worldwide to 1 in 2,000 live births, Rasopathies manifest with often overlapping symptoms that makes the diagnosis difficult (especially in young children), expensive and lengthy.

In collaboration with SW Thames Molecular Genetics Diagnostic Laboratory, St George’s Healthcare NHS Trust, NewGene has developed a comprehensive ‘all in one’ diagnostic screen for all Noonan spectrum disorders. In this assay, the Roche 454 amplicon approach is used to facilitate large scale parallel sequencing of coding regions and splice sites of 11 genes implicated in Rasopathies (PTPN11, SOS1, RAF1, BRAF, MEK1/MAP2K1, MEK2/MAP2K2, SPRED1, CBL, KRAS, NRAS, HRAS) and exon 1 of SHOC2. The combination of next generation sequencing (NGS) and confirmatory Sanger sequencing provides an overall analytical sensitivity and specificity of more than 98%. Since the launch of the test in July 2012 we have analysed DNA samples from 80 patients using this NGS-based assay. We have detected 24 pathogenic variants and 9 variants of unknown clinical significance. This confirmed clinical diagnosis in 30% of tested patients. Segregation studies and RNA splicing investigations carried out by St George’s can help determine pathogenicity of some unclassified variants thus increasing the diagnostic value of this assay. Case studies presented here will further illustrate clinical utility of Noonan Spectrum test. Following the recent discovery of a potential novel gene implicated in Rasopathies, which was announced at the ASHG 2012, the existing assay has now been extended to incorporate screening for
mutations in A2ML1 and whole of SHOC2 coding region. Taking into account the phenotypical overlap of the Legius syndrome with neurofibromatosis type 1, NF1 gene was also included in the new design.

We will introduce the concept of our upgraded Haloplex/MiSeq-based assay and discuss preliminary results of validation of Noonan Spectrum test v2.
SESSION 5: MEDICATION AND PREGNANCY

TRENDS IN MEDICINE USE DURING PREGNANCY IN FINLAND 1996-2010

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The use of medicines during pregnancy is common, but ethical reasons prevent drug safety studies in pregnant women and epidemiological studies on large nation-wide data are needed. The aim of this study was to identify the trends and proportions of medicine use and the degree of safety of medicine use during pregnancy. Additionally, we evaluated how many parturients have chronic diseases and what drugs are used to treat these diseases during pregnancy. Data on parturients (N=859,359) in Finland during the 1996-2010 period were obtained from the Medical Birth Register maintained by the National Institute for Health and Welfare. These data were linked to information on maternal reimbursed drug purchases and maternal eligibility for higher drug reimbursement for certain chronic diseases from the databases of the Social Insurance Institution. Medicine use was common in parturients, with 51% having at least one drug purchase at some point during pregnancy, including 1 month prior to pregnancy. About 30% purchased at least one drug during the first month of pregnancy or one month prior to pregnancy. The percentage of parturients purchasing medicines increased from 49% in 1996 to 59% in 2010. The percentage of parturients with chronic diseases increased from 5.6% in 1996 to 7.7% in 2010. There was also an increase in drug use, for example, the antiepileptic lamotrigine (from <0.01% in 1996 to 0.23% in 2010, the most used antiepileptic). Of the purchased medicines, 34% were known to be harmful to the fetus according to the pregnancy safety classification (FASS) and clearly harmful in 4%. The number of harmful drug purchases decreased with advancing gestation. Monitoring of drug use during pregnancy and lactation, drug safety and possible harmful effects on the fetus are important, and these data show that this can be done efficiently and reliably by combining national registers.
AN EVALUATION OF E-PHARMACIES SELLING THE TERATOGENIC DRUG, ISOTRETINOIN

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Background: The Pregnancy Prevention Program (PPPs) for Isotretinoin was designed to reduce the potential risk of pregnancies among women taking the drug. The program mandates that this teratogenic drug can only be prescribed by, or under the supervision of a specialist with expertise in the use of systemic retinoids for the treatment of severe forms of acne. With the proliferation on e-pharmacies, globally there is now the opportunity for consumers of health to purchase medications online.

Design: A case study was conducted to explore the potential for women of child bearing age to purchase isotretinoin directly from an e-pharmacy without the requisite prescription.

Methods: The key term ‘buy isotretinoin’ was used to identify the first ten unique e-pharmacies from each of the five most common search engines. Fifty sites were evaluated in terms of ‘general website’ and ‘e-pharmacy criteria, and ‘Isotretinoin PPP specific criteria’. Eight purchases of Isotretinoin were attempted from randomly selected illegitimate online pharmacies. The seven samples received were assessed for PPP policy adherence, purchasing procedures, and compound quality.

Main Findings: Forty-three (86%) of the e-pharmacies were illegitimate. The majority of sites did not state that isotretinoin should not be taken if planning or at risk of becoming pregnant (66%, n= 33). Half (n=25) of the websites made no reference to the fact that Isotretinoin can cause birth defects. All 7 samples received were proven to be Isotretinoin. None were received in a properly labelled container with an appropriate patient information leaflet.

Conclusions: Women of childbearing age have the option to self-purchase Isotretinoin directly from websites that do not provide risk assessment, pregnancy prevention education, or warnings of the associated dangers. These findings have implications for the operation and monitoring of PPP, for clinicians, and for the regulation of internet pharmacies.

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LIVING WITH FETAL VALPROATE SYNDROME: EXPERIENCES OF SEVEN YOUNG PEOPLE

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Sodium Valproate (VPA) is the most commonly prescribed drug for primary generalised epilepsy and some women will continue to take VPA throughout their pregnancy, despite the fact that this increases the risk of congenital malformations, delayed neurodevelopment, medical problems and cognitive difficulties. More subtle effects on quality of life have not been studied. In this qualitative research we studied the life experiences of participants with Fetal Valproate Syndrome (FVS). Seven individuals, aged 12½ - 22, with a confirmed diagnosis of FVS, participated in face to face semi-structured interviews. Interview topics included schooling, relationships, life experiences, health perceptions and recognition of the term Fetal Valproate Syndrome. All reported having extra help at school. All were good at Information Technology but many found English skills difficult. Four reported bullying or name calling. Participants generally had close relationships with family members, particularly their mother, and valued parental support. All considered themselves fit and healthy. Significantly, four mentioned hearing problems. The young people's understanding of FVS varied from being fully aware of the term, what it meant and knowing that they had the condition, to not apparently recognising the term. Of the five able to talk about the personal impact, all knew that the cause related to a tablet taken during their mother’s pregnancy. Few spoke about their condition to anyone. Participants generally took a positive outlook to living with the diagnosis, three identifying themselves as special or different and feeling proud. Three participants related moments of personal achievement within the context of FVS adversity. This was despite recognising limitations of their condition and two having faced difficult experiences. This research also demonstrates some challenges of interviewing young people with learning difficulties and how they can be lessened using imaginative visual aids.
S10
THE PREVALENCE AND RISK OF DOWN SYNDROME IN MONOZYGOTIC AND DIZYGOTIC MULTIPLE PREGNANCIES IN EUROPE: IMPLICATIONS FOR PRENATAL SCREENING

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Aim: To determine risk of Down Syndrome (DS) in multiple (monozygotic and dizygotic) relative to singleton pregnancies.

Methods: Population-based prevalence study based on EUROCAT registries in eight European countries. The population was 14.8 million births 1990-2009; 2.89% of which were multiple births. Cases of DS included livebirths, fetal deaths from 20 weeks gestation, and terminations of pregnancy for fetal anomaly (TOPFA). Relative risk (RR) of DS per fetus/baby from multiple versus singleton pregnancies and per pregnancy in monozygotic and dizygotic versus singleton pregnancies calculated by Poisson regression stratified for maternal age, country and time.

Results: adjRR of DS per fetus/baby for cases from multiple versus singleton pregnancies was 0.58 (95%CI 0.53 - 0.62). adjRR of DS per pregnancy for monozygotic versus singleton pregnancies was 0.34 (95% CI 0.25 - 0.44) and for dizygotic pregnancies 1.34 (95%CI 1.23 - 1.46). Under 45 years, RR did not vary with maternal age but was lower for women over 44. 8.71% of pairs where at least one co-twin had DS were concordant for DS.

Conclusion: The risk of DS per fetus/baby is lower in multiple than singleton pregnancies, particularly in monozygotic pregnancies, and particularly for mothers over 44. The risk of DS per monozygotic twin pregnancy is approximately 1/3 that of a singleton pregnancy for a mother of similar age, while the risk per dizygotic twin pregnancy is approximately 1/3 greater than that of a singleton pregnancy for a mother of similar age. These new risk estimates are important for prenatal screening of multiple pregnancies.
ASSESSING THE ROLE OF MULTIPLE PREGNANCIES IN THE ASSOCIATION BETWEEN TETRALOGY OF FALLOT AND ASSISTED REPRODUCTIVE TECHNIQUES: A PATH-ANALYSIS APPROACH

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Objectives: To assess the extent to which the association between assisted reproductive techniques (ART) and the risk of tetralogy of Fallot (TOF) may be mediated by a higher risk of multiple pregnancies associated with ART.

Methods: We conducted a case-control study using data from Paris Registry of Congenital Malformations for the 1987-2009 period and a cohort study of congenital heart defects (EPICARD), including a total of 395 cases of TOF and 4104 malformed controls with no known association with ART. The analysis was based on a path-analysis model using a counterfactual approach, which allows decomposition of the total effect of ART into an indirect effect (that mediated by the association between ART and multiple pregnancies) and a direct effect.

Results: ART (all methods combined) was associated with a 2.6-fold higher odds of TOF after adjustment for maternal and paternal characteristics and year of birth (Adjusted-OR 2.6, 95% CI, 1.5-4.5). Most (79%) of the effect associated with ART was a direct effect (i.e. not mediated by multiple pregnancies), whereas 21% of the effect of ART was due to its association with multiple pregnancies (i.e. the indirect effect). When analyzed separately, intracytoplasmic sperm injection (ICSI) was associated with a 3.5-fold higher odds of TOF (Adjusted OR 3.5, 95% CI, 1.1-11.2); 11% of this effect was mediated through the association of ICSI with multiple pregnancies.

Conclusions: So far, most of the higher risk of TOF associated with ART is a direct effect and only a small proportion of the effect may be mediated by multiple pregnancies. The path analysis approach presented here can be more generally useful for assessing the role of multiple pregnancies in the association between ART and the risk of congenital anomalies or other adverse pregnancy outcomes.
P1
CHANGES IN DOWN SYNDROME CAUSED MORTALITY IN HUNGARY BETWEEN 1980 AND 2006

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Objective: The potential Down syndrome (DS) indicators can be calculated from death statistics. They could be used to describe the public health burden and the effectiveness of care for Down patients. The aims of our study were to (1) assess DS related mortality trends, (2) assess the reliability of data collection methods, and (3) evaluate the usefulness of DS mortality data as public health indicators.

Methods: The usual death certification based mortality data were obtained from the Central Statistical Office. Records with ICD 758 or Q90 as the underlying cause of death were analyzed. We analyzed 914 cases from the 1980-2006 period by the usual mortality indicators.

Results: The DS caused standardized mortality did not change significantly in the study period (1980: 3.89/million, 2006: 3.91/million). The change in the classification from ICD9 to ICD10 in 1996 and the introduction of automatic coding in 2005 for the cause of death did not cause any variation in the registered mortality. More patients lived longer, the mean age at death increased from 2.69 to 38.22 (b=1.022, p<0.001). We noticed that the potential life-years lost decreased from 10,962 in the 1980’s to 2,551 by 2006.

Conclusion: Although DS mortality did not show significant increase during the study period, the patients lived longer. This progress could be explained by enormous development of surgical methods (especially cardiac surgery). Age-at-death can be used to demonstrate the progress in DS patient care rather than the age-standardized mortality measures.
THE FREQUENCY OF CHROMOSOMAL ABNORMALITIES AMONG DYSMORPHIC LIVEBORN CHILDREN IN TUZLA CANTON 2006-2012

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Introduction: The present investigation was conducted as part of a larger retrospective-prospective study over a 15-year period (1997-2002, 2000-2005 and 2006-2012). In this part of the study January 2006-December 2012, the correlation between clinical and cytogenetic findings was determined in 33,205 live borns from all parts of Tuzla Canton (TC) in Bosnia and Herzegovina, who had suspect clinical diagnosis of chromosomal abnormalities. The aim of this study was also to present the trends in the incidence and prevalence of chromosomal abnormalities in newborns in TC and compare it with previous investigations.

Materials and methods: We analyzed medical documentation of children and their parents. Diagnosis was made on the basis of physical examination, ultrasound and radiological examination. Cyto genetic findings confirmed the syndrome.

Results: We found 51 karyotypes with anomalies and excluded two of them as polymorphism. Trisomy 21 was most frequent (72.74%) and was found in 1:1,038 live births (prevalence 0.96‰); one boy had mosaic trisomy 21. Trisomy 18 phenotype was confirmed in one girl (incidence 1:33,205 live births, prevalence 0.03‰), trisomy 13 in two girls (incidence 1:1,603 live births, prevalence 0.06‰), and monosomy X in two girls (incidence 1:8,022 girls, prevalence 0.12‰). The combined incidence of autosomal abnormalities was 1:706 live births (prevalence 1.41‰). The combined incidence of all chromosomal abnormalities was 1:678 live births (prevalence 1.47‰, boys to girls ratio 1.7:1.0). The mean maternal age was 27.97 (range 19-39) years.

Conclusion: The number of births per year shows a declining trend. Maternal age and prevalence of Down syndrome are also decreasing, and other syndromes are very rare. Syndromes often include heart defects and other anomalies. Follow up of children with chromosomal anomalies every 3-6 months during the first two years of life is recommended.
DESCRIPTIVE CASE STUDY OF CARE, SURVEILLANCE AND PREVENTION OF BIRTH DEFECTS IN KIGALI UNIVERSITY TEACHING HOSPITAL

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Introduction: According to the World Health Statistics 2008, about 260,000 neonatal deaths worldwide are caused by congenital anomalies. This figure represents about 7% of all neonatal deaths. This project aimed to describe care, surveillance and prevention measures of birth defects in Kigali University Teaching Hospital. It will focus on understanding the epidemiology of birth defects and mortality in children with birth defects in this hospital.

Methods: A database was created of all birth defects occurring at Kigali University Teaching Hospital over 12 months (2012). The Hospital records were reviewed for demographics, diagnoses, management, outcomes and data analyzed for birth defect related deaths.

Results: Birth defects accounted for 13.60% of 493 infant deaths (67 cases), 64.1% female and 35.9% male, 70.2% premature babies (≤32 weeks), 7.3% infants (5-12 months of age) and 19.6% aged <5 months. Polymalformations were the most common cause of death in overall (85.8%), as well as in premature (89.0%) and term babies (74.1%). Cardiovascular birth defects caused deaths in infants (47.6%). Nervous system birth defects caused death in 33.1%, gastrointestinal birth defects in 17.4%, and urogenital birth defects in 6.2% of cases. Over 50% of birth defect deaths in Kigali University Teaching Hospital were cases transferred from different district hospitals, especially those in Eastern Province and death occurred in surgery department, while 73.7% of these died within 48 hours postoperatively.

Conclusions: Birth defects, especially polymalformations, cardiovascular and nervous system birth defects account for a significant burden of deaths in infants with birth defects in Kigali University Teaching Hospital. Prevention of birth defects and better prenatal care are essential areas to be focused in the time to come.
The objective of the study was detection of congenital malformations as a cause of perinatal mortality. Retrospective analysis of perinatal autopsies performed at Vinkovci General County Hospital, Vinkovci, Croatia, between 1974 and 2012 was performed. Congenital malformations were classified as cardiac, respiratory, urogenital, neural and musculoskeletal. Out of 308 perinatal autopsies performed, congenital malformations caused 8.11% of perinatal deaths. In the 1970's and 1980's, the most frequent lethal congenital malformations were cardiac (70%) causing mostly early neonatal deaths, while during the last 20 years the most common were urogenital and neural congenital malformations (30.8% each) causing stillbirths. As the total number of births and perinatal mortality have decreased, congenital malformations have become an even more important cause of perinatal mortality, especially stillbirths.
CONGENITAL HEART DISEASE IN CHILDREN WITH DOWN SYNDROME

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Objective: The objective of this study was to evaluate the prevalence of congenital heart diseases (CHD) in pregnancies (medically terminated/live births) with Down syndrome (DS) at Department of Gynecology and Obstetrics, Rijeka University Hospital Center, Rijeka, Croatia, in the period from January 2004 to December 2012.

Results: A total of 52 pregnancies complicated with DS were investigated; 31 of them were medically terminated, and there were 21 live born children. CHD was diagnosed in 25 (48.1%) pregnancies with DS. The most common single CHD was ventricular septal defect (VSD), accounting for 40% of all CHD. Out of 15 live born children with DS, atrial septal defect (ASD) was found in 8 (53.4%), atrioventricular septal defect (AVSD) in 4 (26.6%), and VSD in 3 (20%) cases. Early surgical treatment was performed in 5 DS with CHD (3 with AVSD and 2 with VSD); among them, one child (AVSD) required reintervention on the left atrioventricular valve and another (VSD + duodenal atresia) died in the first year of life.

Conclusions: The prevalence of CHD in fetuses and children with DS in our population is 48.1%. Early postnatal diagnosis of CHD in children with DS and timely pediatric and surgical interventions are important for the overall high survival rate of live born children with DS and CHD.
LEARNING ABOUT CONGENITAL HEART DISEASES IN VALENCIA REGION

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Congenital heart diseases (CHD) are the most frequent major congenital anomalies. In the majority of cases, the etiology of CHD is unknown. However, there are some factors that are associated with an increased risk of having these pathologies. The purpose of this study was to estimate the prevalence of major CHD and geographical variation in Valencia Region (VR) among children less than one year old born between 2007 and 2010, as well as to identify associated risk factors. Cases were extracted from the population-based Registry of Congenital Anomalies of VR. Data on live born and stillborn were obtained from the Birth Registry (MetaB) and Perinatal Mortality Registry of VR, respectively. The prevalence and its 95% confidence intervals (CI) were calculated according to sex, birth weight, birth gestational age, mother age, province of residence, and origin country of mother. Adjusted odds ratio (OR) and 95% CI were calculated using the logistic regression model. Geographical pattern was analyzed applying Bayesian methods using municipality as geographical unit. A total of 1,875 children with major CHD were identified, yielding a prevalence of 86 per 10,000 births (95% CI: 82.1-89.9), resulting in 91.9% of affected pregnancies in live births, 7.4% terminated and 0.7% stillbirths. A total of 80.4% of cases occurred as isolated CHD, 10.9% combined with other congenital anomalies, and 8.6% syndromes. CHD was prenatally diagnosed in 17% of cases. Ventricular septal defect was the most frequent lesion, accounting for 27.6% of the total. The prevalence was similar in boys and girls for all CHD, but the prevalence of tetralogy of Fallot, aortic valve defects and patent ductus arteriosus was significantly higher in boys compared with girls, whereas the prevalence of pulmonary valve stenosis was higher in girls than in boys. Multivariate analysis showed an association between CHD and preterm birth (OR=3.5; 95%CI 3.1-3.9) and foreign mother (OR=1.4; 95% CI: 1.3-1.6), the risk of CHD was slightly higher in mothers older than 34 compared with the 16-34 age group (OR=1.1; 95%CI 1.0-1.2), but it was not significant when syndromes were excluded. Geographical differences were found in the prevalence of CHD. Population-based Registries of Congenital Anomalies are a useful information source for surveillance of these pathologies and for identification of geographical areas and higher risk group as the basis for prevention and control of health programs.
POPULATION-BASED CONGENITAL ANOMALIES REGISTRY: VALIDITY OF HOSPITAL DISCHARGE RECORDS AS INFORMATION SOURCE FOR CASE IDENTIFICATION

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Major congenital anomalies (MCA) contribute a significant proportion of perinatal and infant morbidity and mortality. Congenital anomalies (CA) are under rare diseases umbrella, with a prevalence lower than 5/10,000 inhabitants for most of them and they are life-threatening or chronically debilitating diseases. Population-based registries are a powerful tool for surveillance and health service evaluation. Since 2011, the population-based Congenital Anomalies Registry of Valencia Region (CARVR) is member of EUROCAT (the European network of population based registries for the epidemiological surveillance of congenital anomalies). Multiple information sources are used for data collection, with Hospital Discharge Records (HDR) as one of the main tools for case identification. The aim of this study was to assess the validity of HDR for identifying MCA among children less than one year of age, residing in Valencia Region (VR) and born in 2007. An observational epidemiological study was carried out. HDR of 9 VR public hospitals for 2007-2008 were used to identify children less than one year old, born in 2007, residing in VR and with at least one code of CA (codes 740-759 of International Classification of Diseases 9th revision Clinical Modification). Moreover, a sample of 523 children without codes of CA were selected at random from HDR of those hospitals. Sample size was calculated considering a confidence level of 95%, CA proportion of 16% and confidence interval of 3%. Medical Identity Number was used for patient identification and medical histories were reviewed. A total of 2,184 children under one year with CA were identified and 40.3% of them were confirmed as MCA. Medical history was not available in 53 (2.4%) cases. In patient sample, 4 (0.8%) CA cases were identified as MCA. The positive predictive value was 58% (95% CI: 56-60) and the negative predictive value was 99.2% (95% CI: 98.9-99.6). The CARVR registered 1,344 MCA in 2007 (prevalence of 244 x10,000 births). HDR of the 9 public hospitals included in the study identified 65.5% of the total and 81% of live births. Termination of pregnancies for fetal anomaly and stillbirths was not identified by HDR. The selection of HDR including at least a code of congenital anomaly provides identification of the majority of MCA among live births. Nevertheless, it is necessary to include algorithms in the selection procedure in order to improve efficiency.
A STUDY ON CONGENITAL LIMB ANOMALIES IN NORTHERN CROATIA

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Background: Congenital limb anomalies present a heterogeneous group of disorders of limb development. Information on their prevalence and associated anomalies is important for etiologic research, planning of treatment and appropriate health services. The purpose of this study was to determine the prevalence, clinical and epidemiological characteristics of limb defects in northern Croatia.

Patients and methods: We reviewed limb anomalies reported among 97,108 births in northern Croatia during the 1996-2010 period. The analysis included prevalence, sex distribution, frequency of associated anomalies, time at diagnosis, type of birth, and familial occurrence.

Results: A total of 352 children were found to have limb defects. The overall birth prevalence was 3.8 per 1,000 births. The most frequent were hip dislocation/dysplasia (23%), talipes equinovarus (21.6%), limb reduction defects (10.5%), and syndactyly (8.2%). Most patients were diagnosed at birth (65.8%), or in the first week of life (26.7%). Prenatal ultrasonography detected 5.8% of cases. In all of them, additional anomalies or skeletal dysplasia were present. Six out of 19 prenatally detected cases were terminated. There were four stillbirths, 342 live births and six neonatal deaths. The majority of limb defects were isolated (90.9%). A smaller portion of children had associated anomalies (5.9%), or were part of a recognized condition or chromosomal anomaly (3.2%). Familial occurrence was recorded in 12 cases.

Conclusion: A child born with a limb anomaly is easily identified at birth because the physical abnormality is usually apparent. Compared to the average EUROCAT prevalence (4.9 per 1,000) for the same period, northern Croatia has a relatively low prevalence of all types of limb defects with the exception of hip dislocation/dysplasia, which has a prevalence above the EUROCAT average, probably due to the universal neonatal hip screening.
Background: Orofacial clefts are major congenital anomalies that have significant lifelong morbidity and complex etiology. The prevalence of orofacial clefts varies from 1 in 400 to 1 in 2,500 births, depending on geographical origin, racial/ethnic background and socioeconomic status. The purpose is to describe the epidemiology of orofacial clefts in northern Croatia.

Patients and methods: We studied orofacial clefts identified among 97,108 births in northern Croatia during the 1996-2010 period. The analysis included prevalence, sex distribution, frequency of associated anomalies, time at diagnosis, type of birth, and familial occurrence.

Results: Among 97,108 births, 133 cases of orofacial clefts were detected, yielding a prevalence of 1.36 per 1,000 births. A significant (p=0.03) increase in the prevalence was observed in the 2006-2010 period. There were 78 (58.6%) cases of cleft lip with or without cleft palate (CL(P)) and 55 (41.4%) cases of cleft palate (CP). The majority of patients were diagnosed at birth (92.3%), while only 10 (7.7%) were suspected prenatally. A predominance of males among CL(P) and of females among CP was observed. There were 131 live births, one stillbirth and one termination of pregnancy. A total of 119 (89.5%) cases occurred as isolated and 14 (10.5%) were associated with other anomalies, recognized syndromes or chromosomal aberrations. There were 6 (4.5%) familial cases.

Conclusion: Orofacial clefts affect 1 in 730 births in northern Croatia. It is in accordance with the average prevalence in EUROCAT registries (1 in 690) for the same period, but significant differences in the prevalence between registries and within countries have been noted in Europe indicating the possible genetic and environmental influences. The recent increase in the prevalence rate needs further follow up.
CONGENITAL PATHOLOGY IN UKRAINE

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Introduction: The structure and prevalence of birth defects (BD) was estimated among live borns, still borns and genetically caused abortions. Developmental disability and BD caused mortality was estimated among children 0-17 years old.

Materials: Information was obtained from annual reports of medical, genetic and obstetric departments to the Ministry of Health of Ukraine, including the number of live born children, stillbirths and genetically caused abortions; live borns and stillbirths with BD during the 2002-2011 period. Developmental disability and BD caused mortality was estimated by the State Statistics Committee of Ukraine data, including information on the number of disabled children (2002-2010), children who died from different diseases and BD (0-17 years old, 2007-2011).

Results: Among live borns, the BD structure was as follows: bone and muscle deformities (ICD-X: Q65-Q79) 33.40±0.15% (congenital hip dislocation, 13.57±0.18%); cardiovascular system (Q20-Q28) 19.94±0.12%; genitals (Q50-Q56) 15.54±0.11%; chromosomal anomalies (Q90-Q99) 4.40±0.06%; nervous system (Q01-Q07) 3.24±0.06%; etc. BD prevalence was 22.76±0.07‰ (bones and muscles 7.60±0.04 ‰; cardiovascular system 4.54±0.03‰; genitals 3.54±0.03‰; chromosomal anomalies 1.00±0.01‰; Down syndrome 0.87±0.01‰; nervous system 0.74±0.01‰; and spina bifida 0.30±0.01‰). Among live borns, stillbirths and genetically caused abortions, BD prevalence was 26.83±0.08‰ (cardiovascular system 4.90±0.03‰ and nervous system 1.25±0.02‰). There were essential distinctions between BD prevalence in different regions; BD prevalence decreased with years. BD specific gravity was 26.80±0.11% in primary disability structure (it increased from 22.7% to 30.3%). General children’s mortality was 0.96±0.01‰ (mortality from all BD 0.19±0.01‰; from nervous system BD 0.05±0.01‰; and from cardiovascular system BD 0.11±0.01‰).

Conclusions: BD pose a very important social problem in Ukraine. BD are not diagnosed and registered correctly.
PREVALENCE OF CONGENITAL HEART DISEASES IN RIJEKA UNIVERSITY HOSPITAL CENTER, RIJEKA, CROATIA: AN EPIDEMIOLOGICAL STUDY 2007-2012

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Objective: Congenital heart diseases are one of the most common causes of morbidity and mortality in neonates and infants. The aim of this study was to assess the prevalence of certain types of congenital heart diseases, time to diagnosis, maternal age and family history of children born at Rijeka University Hospital Center, Rijeka, Croatia, during a six-year period.

Methods: Patient information for this retrospective study was collected by the forms based on the EUROCAT study and protocols for children born with a diagnosis of congenital heart diseases during a six-year period, from January 1, 2007 to December 31, 2012, at Rijeka University Hospital Center in Rijeka. We analyzed the type of heart disease, time to diagnosis, survival rate for newborns, events preceding and during pregnancy in mother and father, their age, and family history.

Results: During the study period, there were 18,666 births and a total of 18,930 live-born children, of which 185 patients were diagnosed with congenital heart disease, accounting for 0.97% of the live-born children. This result is a little higher than the national average for the five-year period 2002-2007, when heart diseases had a prevalence of 0.7%. The most common diagnoses were atrial septal defect (87 newborns), ventricular septal defect (75 newborns) and open arterial duct (25 newborns). This result also varies from the national average for the 2002-2007 period, when the most common heart defect was ventricular septal defect. Seven children did not survive the first week, and for five children data were not available.

Conclusion: The importance of a registry of this kind is a basis for various epidemiological studies as well as for planning and constructing prenatal and postnatal screening and algorithms for diagnosis, therapy and prevention.
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CONGENITAL HEART ANOMALIES IN THE VALENCIAN REGION (SPAIN) AND INDUSTRIAL POLLUTION

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Congenital heart anomalies (CHA) are an important public health threat to the quality of life of affected families. The etiology of most CHA is unknown, suspecting an interaction of multiple genetic and environmental factors, including emissions of polluting industries. The aim was to analyze the relationship between CHA and industrial pollution in the municipalities of the Valencia Region (VR), Spain. An ecological study was designed to analyze CHA prevalence in municipalities of VR during the 1999-2008 period. CHA cases were extracted from hospital records. Children younger than one year, born in VR during the study period with at least one diagnosis coded as CHA (ICD-9: 745-747) were selected. Health identity number was used for child identification and only the first hospital discharge with CHA was included in the analysis. Exposure to industrial pollution was estimated on the basis of distance between municipalities and industries (obtained from the European Pollutant Release and Transfer Register (E-PRTR). Bayesian hierarchical models were used to estimate the effect of the exposure on CHA prevalence. We considered the risk surface as a constant plus a Gaussian function decreasing with distance from each industry. The remaining overdispersion was modeled by means of two random effects (spatial and heterogeneous) for every municipality. A total of 6,351 CHA were identified and 680 industries located on 541 VR municipalities and the surrounding 50 km area were considered. Although geographical patterns had been identified, no significant relationship was found between CHA and the distance to industrial source ($\beta=0.084$ (Credibility Interval (CI) 95%: -0.168; 0.531). No association was found between CHA and distance to industries. The use of CHA registry data, analysis of other types of CHA, use of additional information (socioeconomic, meteorological, etc.), and the extension of the study period to improve statistical power are considered as future investigation lines. Funded: FIS PI10/01676
CONGENITAL ANOMALIES IN A HIGH ENVIRONMENTAL RISK AREA. A CASE CONTROL STUDY IN BRINDISI (SOUTHERN ITALY)

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Maternal exposure to ambient pollution has been increasingly linked to the risk of congenital anomalies (CAs) in fetus and newborns. Recently, a descriptive study (Gianicolo et al., 2012) revealed an increased prevalence of total CAs and in particular, congenital heart diseases (CHDs) and ventricular septal defects (VSDs) in Brindisi, both at local level and in comparison with the pool of EUROCAT registries. Due to the presence of many sources of pollution near the urban area, in the 1980s, Brindisi and surrounding municipalities were identified by the Italian Ministry of Environment as an “area at high risk of environmental crisis”. Epidemiological studies have revealed several critical situations in terms of increasing rates of mortality and morbidity directly or potentially associated with environmental and occupational exposure to pollutants. This population-based case-control study investigated the association of maternal exposure to air pollutants sulfur dioxide (SO2) and total suspended particulate matter (TSP) with the risk of CA. Cases were newborns to mothers residing in Brindisi between 2001 and 2010, up to 28 days of age, and discharged with a diagnosis of CA. Cases and controls were individually matched according to sex, socioeconomic status of the census area of residence of the mother, and year of conception. Four controls were extracted for each case. Concentration data from monitoring stations data were used to estimate air pollution exposure. Each case and control were assigned pollutant concentration values (weeks 3-8 of pregnancy). Exposure as both continuous and categorical variable was considered and a conditional logistic regression model was constructed to quantify the odds ratios of exposure to air pollutants and the occurrence of total CAs, CHDs and VSDs. We found exposure to SO2 to be associated with CHDs and VSDs. Findings for TSP were less consistent.
TIME SERIES ANALYSIS OF THE EFFECT OF PANDEMIC INFLUENZA SEASON ON CONGENITAL ANOMALY PREVALENCE IN EUROPE

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Background: In the context of the European surveillance for congenital anomalies (EUROCAT) surveillance response to the 2009 H1N1 influenza pandemic we sought to assess the impact of the 2009 influenza pandemic on congenital anomaly (CA) prevalence in Europe. We also explored the impact of seasonal influenza and of pandemic influenza vaccination policy for 1st trimester pregnant women.

Methods: We conducted an ecological times series analysis in 13 European countries. Our dataset included 22,086 cases of CA from EUROCAT, conceived from January 2007 to March 2010, and corresponding birth denominators. Influenza exposure data was based on weekly, country-specific WHO surveillance data, applied to CA-specific critical periods. In our Poisson regression model, we utilized a categorical variable for pandemic and seasonal influenza activity, a categorical variable representing pandemic vaccination policy and a seasonality function.

Results: No evidence was detected for an increase in CA during 2009 pandemic influenza season (ARR 1.03, 95% CI: 0.97-1.09) and during 2007-2008 and 2008-2009 influenza seasons (ARR 1.04, 0.98-1.10). No evidence was detected for an increased prevalence of neural tube defects (ARR 0.91, 0.70-1.19) among pregnancies exposed to influenza season. We did detect increased prevalences for situs inversus for all influenza seasons combined (ARR 2.06, 1.02-4.15), transposition of the great vessels (ARR 1.57, 1.17-2.11) and some other CA. No evidence was detected for an eff ect of pandemic influenza vaccination policy on congenital anomaly prevalence.

Discussion and conclusion: Our data do not suggest an overall eff ect of pandemic or seasonal influenza on CA prevalence. Exposure to influenza season during certain periods in pregnancy could potentially cause an increase in situs inversus and related anomalies, which we have previously found to show a seasonal peak during influenza season before this study period. This increase could be due to influenza, fever, antivirals or antipyretics, but needs confirmation in other studies.
PREVALENCE OF FETAL ALCOHOL SYNDROME AND PARTIAL FETAL ALCOHOL SYNDROME IN NORTHWESTERN CROATIA

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We present results of the epidemiological study of fetal alcohol syndrome (FAS) and partial fetal alcohol syndrome (PFAS), performed with the aim to estimate the prevalence of these congenital syndromes as well as maternal pregnancy alcohol drinking habits and characteristics in a sample of schoolchildren from northwestern Croatia. The study was performed among schoolchildren attending elementary school 1st to 4th grade and their mothers from the capital city of Zagreb and rural Krapina-Zagorje County. The study involved a sample of 2022 children, including 912 children from Zagreb schools and 1,110 schoolchildren from Krapina-Zagorje County. We used active case ascertainment method with passive parental consent and Clarified Institute of Medicine criteria. Investigation protocol involved clinical examination of schoolchildren and data collection from their mothers. Mothers of 1,492 (73.8%) schoolchildren answered the questionnaire and 1,290 (63.8%) schoolchildren attended clinical examination. Clinical features of FAS were observed in 17 (1.3%), of PFAS in 58 (4.5%), and of FAS/PFAS in 75 (5.8%) out of 1,290 children. Pregnancy alcohol consumption was confirmed by 12.8% of mothers and 2.9% admitted at least one binge episode during pregnancy. The study confirmed an association between pregnancy alcohol consumption and clinical signs of FAS/PFAS. The study also revealed differences between investigated groups of mothers. A higher prevalence of binge drinking and smoking during pregnancy as well as a significant association between smoking and drinking during pregnancy was observed in Zagreb in contrast to rural Krapina-Zagorje County. Based on the 63.8% participation rate in clinical examination, the estimated prevalence of FAS is 13.1, of PFAS 44.9 and of FAS/PFAS 58.1 per 1,000 schoolchildren. The high rate of pregnancy alcohol consumption and high FAS/PFAS prevalence observed in this study revealed that FAS is a serious health problem that calls for development of appropriate preventive strategies.
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SAFETY OF NEURAMINIDASE INHIBITORS DURING PREGNANCY: A COMPARATIVE STUDY IN EFEMERIS DATABASE

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Aim: To compare birth outcomes between exposed and unexposed women to the antiviral medications oseltamivir or zanamivir during pregnancy.

Methods: This observational study compared exposed and unexposed pregnant women in EFEMERIS. EFEMERIS is a database including prescribed and dispensed reimbursed drugs during pregnancy (data from Caisse Primaire d’Assurance Maladie of Haute-Garonne) and outcomes (data from Maternal and Infant Protection Service and from Antenatal Diagnosis Centre). Women who delivered from July 1, 2004 to December 31, 2010 in Haute-Garonne and were registered in the French Health Insurance Service were included in EFEMERIS database. We compared pregnancy outcomes and newborn health between women exposed to oseltamivir or zanamivir during pregnancy and unexposed women. Unexposed women were individually matched to exposed women by maternal age, month and year of delivery, or pregnancy termination. Malformations were classified according to EUROCAT classification.

Results: A total of 338 (0.58% of EFEMERIS women) women exposed to neuraminidase inhibitors and compared with 676 unexposed women. Only 1 pregnant woman received zanamivir and 337 received at least one prescription of oseltamivir. The mean number of drugs taken during pregnancy was higher in the exposed group (12.5 ± 7 vs. 9.7 ± 6.9; p<10^-4). The pregnancies led to 96.4% vs. 93.3% of live births (p<10^-4) in exposed and unexposed group, respectively. No increased risk of preterm birth associated with these antiviral drugs during pregnancy was found (adjusted OR =0.67; 95% CI=0.23-1.80). When exposure during organogenesis was considered, 1 case (2.0%) among those exposed and 1 (1.0 %) among the unexposed was observed (crude OR=2.0, 95% CI=0.13-32.00).

Conclusion: We found no increased risk of adverse pregnancy outcomes (preterm delivery, low birth weight, neonatal pathology and congenital malformation) among women exposed to oseltamivir compared with unexposed pregnant women.
We have established a rodent organ culture model at the air liquid interface to investigate the influence of various factors upon mammalian development in its most critical periods. Early postimplantation embryos or parts of older embryos can be cultivated up to two weeks in the serum-supplemented or serum-free media. During the usual two-week culture period, overall growth can be measured by ocular micrometer. After fixation, the expression of the Proliferating Cell Nuclear Antigen and differentiation of various tissues such as epidermis, neural tissue, cartilage, myotubes, etc. can be assessed by light microscopy. All end points can be statistically evaluated. Epigenetic drugs such as the DNA demethylating agent 5-azacytidine and esiRNA against stemness gene RNAs impaired growth. On the other hand, antioxidant PBN or a specific hyperthermia treatment were able to ameliorate growth of the gastrulating rat embryo. In the serum-free model of embryo development, changes of differentiation were more clear-cut than in serum-supplemented medium (e.g., with teratogen 5-azacytidine). Results obtained with this ex vivo model, in which teratogenic factors are applied directly to the embryo thus avoiding the maternal effect, are of importance for investigation of embryotoxicity and teratogenicity and their prevention.
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PREGNANCY OUTCOME IN WOMEN EXPOSED TO DOPAMINE AGONISTS DURING PREGNANCY: A STUDY IN EFEMERIS DATABASE

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Aim: Little is known about the possible effect of dopaminergic agonists on embryofetal development. The aim was to describe pregnancy outcomes in women exposed to prescription of dopamine agonists in EFEMERIS, a cohort of French pregnant women.

Methods: An "exposed-non exposed" study was conducted in EFEMERIS cohort (database including prescribed and dispensed drugs during pregnancy and outcomes, 57,408 mother-outcome pairs included between 2004 and 2010). Women who received a dopamine agonist drug during pregnancy were considered as exposed to dopamine agonist drugs and classified in the "exposed group". They were individually matched to 2 "unexposed" women. We compared adverse fetal outcomes in the two groups using conditional logistic regressions.

Results: A total of 183 (0.3%) women were prescribed at least one dopamine agonist during pregnancy. Bromocriptine was the most prescribed drug (65%), followed by cabergoline (20%) and quinagolide (10%). Most of the indications (67%) were hyperprolactinemia; 75% of dopamine agonist prescriptions were issued during the first trimester of pregnancy. Prescriptions strongly decreased during the second trimester (8.8%). There was no difference between the two groups concerning pregnancy history and demographic data. After adjustment for potential confounders, the risks of pregnancy termination and preterm birth were significantly increased after exposure to dopamine agonist drug during pregnancy with the respective prevalence odds ratio of 3.7 (95% CI 1.8, 7.4) and 2.7 (95% CI 1.04, 7.0). The prevalence of birth defect and low birth weight was not statistically different between the two groups. No difference in psychomotor development at 9 and 24 months of babies was observed.

Conclusion: The results of this study suggest that fetal exposure to dopamine agonist drugs may increase the risk of adverse fetal outcomes.
SAFETY OF INFLUENZA AH1N1 PANDEMIC VACCINATION DURING PREGNANCY: A COMPARATIVE STUDY IN EFEMERIS DATABASE

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Aim: To compare birth outcomes between exposed and unexposed women to influenza AH1N1 pandemic vaccine during pregnancy.

Methods: This observational cohort study compared exposed and unexposed pregnant women in EFEMERIS. EFEMERIS is a database including prescribed and dispensed reimbursed drugs during pregnancy (data from Caisse Primaire d’Assurance Maladie of Haute-Garonne) and outcomes (data from Maternal and Infant Protection Service and from Antenatal Diagnosis Centre). Women who delivered between October 21, 2009 and November 30, 2010 in Haute-Garonne and were registered in the French Health Insurance Service were included. We compared pregnancy outcomes and newborn health between women exposed to AH1N1 vaccine during pregnancy and unexposed women. Unexposed women were individually matched to exposed women by month and year of delivery or pregnancy termination. Malformations were classified according to Eurocat classification.

Results: A total of 1,645 (13.6%) women exposed to pandemic AH1N1 vaccine were compared with 3,290 unexposed women. Most were exposed to the vaccine in December 2009 (61%) and Panenza® was used in 92.7% of cases. The mean maternal age was 31.4 ± 4.3 in the exposed group and 29.9 ± 5.4 in the unexposed group (p<10^-4). The pregnancies resulted in 99.2% and 95.2% of live births in the exposed and unexposed group, respectively; the difference was not significant (adjusted HR=0.56, 95% CI=0.31-1.01). When exposure during organogenesis was considered, no increased risk of congenital malformations was found (adjusted OR=0.73; 0.10-2.34).

Conclusion: We found no increased risk of adverse pregnancy outcomes (pregnancy termination, preterm birth, low birth weight, neonatal pathology and congenital malformation) among women exposed to Panenza® compared to unexposed pregnant women.
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VENOTONICS IN PREGNANCY: A COMPARATIVE STUDY IN EFEMERIS DATABASE

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Aim: To investigate the potential adverse drug reactions of venotonics in pregnancy.

Methods: This observational study compared exposed and unexposed pregnant women in EFEMERIS. EFEMERIS is a database including prescribed and dispensed reimbursed drugs during pregnancy (data from Caisse Primaire d'Assurance Maladie of Haute-Garonne) and outcomes (data from Maternal and Infant Protection Service and from Antenatal Diagnosis Centre). Women who delivered from July 1, 2004 to December 31, 2007 in Haute-Garonne (time period when venotonics were still reimbursed) and were registered in the French Health Insurance Service were included. We compared pregnancy outcomes and newborn health between women exposed and unexposed to venotonics during pregnancy. Malformations were classified according to Eurocat classification.

Results: A total of 8,998 (24.3%) women exposed to venotonics during pregnancy were compared with 27,963 unexposed women. The most widely used venotonics were diosmin, hesperidin, and troxerutin. The mean age of the mothers was 31.2 ± 4.8 years in the exposed group and 30.0 ± 5.1 in the unexposed group (p<10^-4). The mean number of drugs taken during pregnancy was higher in the exposed group (12.8 ± 8 vs. 8.8 ± 7; p<10^-4). Pregnancies led to 98.4% vs. 93.6% of live births and 0.2% vs. 0.2% of postnatal deaths in exposed and unexposed group, respectively. When only exposure to venotonics during organogenesis was considered, 39 (3.4%) congenital malformations were observed in the exposed group versus 789 (3.0%) in the unexposed group (p=0.39). There was no difference in the rate of neonatal pathologies between the exposed and unexposed group (5.7% vs. 6.4%, adjusted OR=1.07 (0.95-1.20).

Conclusion: We found no increased risk of adverse pregnancy outcomes (neonatal pathology and congenital malformation) among women exposed to venotonics compared with unexposed pregnant women.
IMPACT OF ANTIPEPTIC DRUGS ON MATERNAL REPRODUCTIVE HEALTH, PREGNANCY, DELIVERY AND NEWBORN’S OUTCOME

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The use of antiepileptic drugs (AED) in women influences their reproduction, conception, pregnancy, lactation, as well as the unborn child. Our aim was to compare maternal and neonatal data of women who had active epilepsy and were using AED before conception and throughout pregnancy – women with active epilepsy (WWAE). Medical records of 166 singleton pregnancies of 164 WWAE were retrospectively and prospectively reviewed for a 15-year period (1998-2012). Demographic, obstetric, newborn and AED related data were evaluated and compared with 240 singleton pregnancies in unaffected controls. The data retrieved were comprehensive due to structural electronic medical history database of over 500 variables, kept at University Department of Gynecology and Obstetrics, Rijeka, Croatia. There were 164 WWAE with 166 pregnancies. The mean age at onset of epilepsy was 16.4 years and 65% had epilepsy for longer than 20 years. There were 73% of women on monotherapy, 59% of them using traditional AED, mostly carbamazepine and valproic acid. Among WWAE on polytherapy, 86% had at least one traditional AED in combination. The mean age of women at the time of delivery was 28 years. No statistically significant difference was found in gynecologic history, number of previous spontaneous and artificial abortions, or number of previous deliveries. In 166 pregnancies, there were no differences in pregnancy induced hypertension, bleedings or infection during pregnancy. WWAE had significantly more fetal ultrasound screenings during pregnancy than unaffected women. Maternal and fetal complications during labor were the same in both groups, and there were no differences in the type of delivery. Postpartum complications were the same in both groups. There were no differences in newborn data (birth weight, birth length, head circumference, gestational age, Apgar score at 1st and 5th minute, number of small for gestational age infants, and admission to neonatal unit). Breastfeeding was less frequent in WWAE as compared with unaffected women (71% vs. 92%), the difference being statistically significant. There were 7 (4.2%) newborns with congenital anomalies in WWAE and 4 (1.6%) in control group, which was not statistically significant. However, there were 2 artificial abortions in WWAE due to fetal neural tube defect. WWAE may be informed on the fact that they do not face an increased risk of several important adverse obstetric outcomes such as spontaneous abortion, pregnancy induced hypertension, premature labor, or cesarean section.
contrast to current opinion, this study showed low birth weight to be about twice as common in WWAE offspring and that neonates had an increased risk of early neonatal adverse outcome. The results obtained confirmed that congenital malformations were more common in children born to WWAE than in general population. During the 15-year period, we observed an increase in the use of newer AED during pregnancy, thus increasing the prevalence of breastfeeding and use of folic acid during pregnancy in WWAE.
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A CROATIAN GIRL WITH RETT SYNDROME AND NOVEL MUTATION ON EXON 4 - 25BP DELETION (C.881-905DEL25) OF MECP2 GENE

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Purpose: To present the genetic and clinical features of a girl with Rett syndrome. Rett syndrome is a pervasive developmental disorder caused by mutations in the X-linked methyl-CpG-binding protein 2 (MECP2) in the majority of cases. It is predominantly found in females with normal development prior to the onset of symptoms at 7-18 months of age; epilepsy is considered as a major problem.

Methods: Retrospective review of data, electroencephalography and treatment were performed in a 20-year-old girl previously diagnosed with MECP2 mutation.

Results: The girl was born in a healthy family as the fourth child, after uneventful pregnancy, delivery and perinatal period. Growth and psychomotor development were normal, except for delayed speech. First absence seizure occurred at the age of 3 years during a bath. Electroencephalography (EEG) showed focal discharges and therapy with carbamazepine was initiated. After frequent absences, EEG showed generalized discharges and valproic acid was added. At the age of 3.5 years, autistic behavior was observed, followed by rapid mental deterioration, loss of speech and motor skills, with periods of hyperventilation and fear, rarely ‘hand-washing’ movements appeared. After exclusion of a wide spectrum of neurometabolic diseases, at the age of 5 years, genetic analysis resulted in a mutation on exon 4 – 25bp deletion (c.881-905del25) of MECP2 gene. Until now, multiple epileptic seizure types occurred daily, refractory to all antiepileptic polytherapy with normal video EEG background; she is able to walk slowly on wide based gait, she is atactic and spastic.

Conclusion: In our girl, the onset of symptoms began much later than usually in cases of Rett syndrome, with drug resistant epilepsy occurring daily; unexpectedly, she is able to walk at the age of 20 years. There may be a genotype-phenotype correlation.
WHY ARE THE PREVALENCE RATES OF TRISOMY 13 FALLING IN OLDER MOTHERS?

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Aim: To describe trends in maternal age related prevalence rates of Patau syndrome (trisomy 13) compared with other common trisomies.

Method: CARIS data was used to estimate prevalence rates of Patau syndrome (T13) among pregnancies ending in Wales for two maternal age groups (under 35 and 35 yrs+). All pregnancy outcomes were included for the years 1998 to 2011 and annual or 3 yearly prevalence expressed as a function of all live and still births. Rates and trends for T13 were compared to similar estimates for Trisomy 21 and Trisomy 18.

Results: For all three trisomies studied, rates for younger mothers are lower than for older mothers and have remained stable over the time period of study, with no overall trend identified.

Rates for older mothers are higher than for younger mothers for all three trisomies. For T21 and T18 there is no clear trend demonstrating a change in prevalence.

For older mothers of babies with T13, there has been a steady downward trend in prevalence over the time period studied.

Discussion: The finding of decreasing prevalence rates for T13 among older mothers in Wales was unexpected. Potential explanations of this finding are unclear but could include variation in paternal age, parity and fetal sex. These factors are examined together with maternal medical history, assisted conception and folic acid usage.

Conclusions and Recommendations: The finding of decreasing prevalence of T13 among older mothers is unexpected. CARIS will be interested to receive reports from other registers to see if this finding has been replicated elsewhere.
A CASE OF FULL MONOSOMIC TURNER SYNDROME ASSOCIATED WITH AGENESIS OF CORPUS CALLOSUM AND COLPOCEPHALY

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Introduction: Turner syndrome (TS) is a result of partial or complete absence of one X chromosome, occurring in about 1 per 2,000 live born girls. It can cause a variety of medical and developmental problems. Some signs and symptoms of TS are seen more frequently, including facial appearance, short stature, growth failure, lymphedema, skin and endocrine problems, and congenital malformations of different organ systems. Among them, congenital malformations of the central nervous system (CNS) are very rare.

Case report: We report on a female infant aged 5 months with full monosomic 45, X karyotype. She was born at term by cesarean section as the third child in the family with two healthy children. Apgar score in the first and fifth minute was 4/6. Her birth weight was 3650 g, birth length 54 cm, and head circumference 35 cm. On physical examination in our hospital, she showed disproportionate growth, mild residual puffiness of the dorsum of the hands and feet, capillary hemangiomas on the nose, forehead and occiput, short neck, hypertelorism, periorbital fullness of subcutaneous tissues, epicanthus, long eyelashes, depressed nasal bridge, low posterior hairline, low set ears, relatively small mandible, narrow palate, laryngeal stridor, widely spaced nipples, loose redundant skin, deep sacral dimple and hypotonia. Echocardiography showed bicuspid aortic valve. Agenesis of corpus callosum (ACC) and colpocephaly were confirmed by ultrasonography and radiographic investigation. In the next few months, she was hypotrophic and slightly hypotonic. She had gastroesophageal reflux, laryngeal stridor, increased sweating, respiratory infections, airway obstructions and feeding problems.

Conclusion: Congenital malformations of the CNS associated with TS are very rarely reported. To our knowledge, only two cases of ACC associated with TS but without colpocephaly have been reported previously, therefore additional genetic research is needed.
Crisponi syndrome was first described by Giangiorgio Crisponi in 1996 and since then it has been reported in Italy, India, Japan, Turkey and Saudi Arabia. The syndrome may present at birth, or may even be picked up prenatally by ultrasonography with isolated 'sign of the horns'. Neonatal signs include extensive muscular contractions in the face after minimal stimuli, which become more obvious during crying, anhidrosis and camptodactyly. A hospital based surveillance project was conducted in Prince Sultan Military Medical City in Riyadh, Saudi Arabia. We diagnosed two patients with Crisponi syndrome based on clinical presentation. Molecular testing done at Bioscenthia lab confirmed the CRLF1 gene in novel mutation. From these two patients, another 11 undiagnosed relatives were identified and molecular diagnosis was obtained for some of them. Five of these patients had 11 ribs only and two had eye problems (retinoblastoma, corneal ulcer). Crisponi syndrome is a severe autosomal recessive condition that was considered rare, but seems to be underestimated in the Saudi population. Our patients have a novel mutation. Some of them had new clinical findings, and prognosis differed from those described in the literature, as most of our patients had normal intelligence and survived into adulthood. We will present 13 cases, describing clinical findings, outcome, and the possible early detection methods as well as preventive measures in a population with high inbreeding.
CONGENITAL ANOMALIES IN PATIENTS WITH SUBMICROSCOPIC CHROMOSOME ABNORMALITIES

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Background: Studies indicate that 4%-9% of subtle chromosome rearrangements can be detected in children or adults with congenital anomalies (CA). The aim of this investigation was to determine the type and frequency of the main subgroups of CA in 72 patients with clinically relevant copy number variants (CNV).

Methods: All patients were evaluated by clinical geneticists before genetic testing, including complete clinical workup. The analysis of CNV was conducted using Multiplex Ligation-dependent Probe Amplification (MLPA) and/or FISH (Fluorescence in situ Hybridization) technique.

Results: Study group consisted of 72 patients with clinically significant CNVs (22 patients with 22q11.2 deletion, eight patients with Williams Beuern syndrome, five with Sotos and Prader Willi syndrome, three patients with Angelman, Wolf-Hirschhorn, and 17q11.21 microdeletion syndrome, two cases of Cri du chat syndrome, one case of Langer Giedion, Phelan-McDermid and del15q24 syndromes, and 18 cases with various subtelomeric rearrangements. The most common CA were different mild skeletal defects present in 37 (51%) patients, followed by congenital heart defects (n=34; 47%), central nervous system (n=32; 44%), urinary (n= 22; 31%) and genital (n=12; 17%) anomalies. More than one CA was found in 32% of cases.

Conclusion: Recurrent CNVs are found in a significant proportion of patients with CAs. Because congenital anomalies are often the first presenting symptom, screening for recurrent CNV with one of the available molecular methods in patients with CAs can lead to early syndrome diagnosis, detection of comorbidity, and appropriate counseling and testing of relatives at risk.
GENETIC CAUSES OF CONGENITAL ANOMALIES IN THE PLEVEN REGION – A REGISTRY-BASED STUDY

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Aim: The aim of the study was to investigate the role and prevalence of the genetic (chromosomal, single gene, multifactorial) causes of congenital anomalies (CAs) in the Pleven region, Bulgaria.

Methods: The source of data was the population-based registry of CAs using criteria according to EUROCAT recommendations. During the 1988-2006 period, 47,622 births were surveyed. A total of 1,225 cases of CAs (ascertained in live births, fetal deaths 20 weeks of gestation, and terminations of pregnancy after prenatal diagnosis) were studied for identification of the main causes (genetic, environmental).

Results: The total prevalence of CAs was 25.72 per 1,000 births. The most common (40% of all cases) CAs were isolated anomalies with multifactorial etiology (such as congenital heart disease, neural tube defects, cleft palate and lip), with a prevalence rate of 10 per 1,000 births. Chromosomal abnormalities accounted for 8% of all CA cases, with a prevalence rate of 2 per 1,000 births. About 14% of all CAs were due to single gene defects and showed prevalence of 3.5 per 1,000 births. Well-established environmental causes were infrequent (7% of all cases of birth defects), and the etiology of one-third of the CAs was unknown or unclear.

Conclusion: The genetic factors take part in the etiology of approximately 62% of all CAs. The high proportion of genetic causes emphasizes the important role of the genetic counseling service as an integral part of preventive medical care.
EVALUATION OF CHROMOSOMAL MOSAICISM BY aCGH AND MLPA: MOLECULAR CHARACTERIZATION OF MOSAIC RING CHROMOSOME 22

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The clinical phenotype of 22q13.3 deletion syndrome may include different clinical features like developmental delay, dysmorphic face and autistic-like behavior. In case of mosaic ring chromosome 22, frequently associated with partial monosomies, variable clinical manifestations may be seen. These are thought to be due to different sizes of deleted subregions at 22qter and the grade of mosaicism. The size of the deletion may range from none at all in asymptomatic cases, to 100 kb and more than 9Mb in symptomatic ones. In some cases, mosaicism may go undetected as the presence of normal cells can mask the presence of abnormal cells; also, the size of mosaics can vary in different tissues of the patient’s body. To evaluate the sensitivity of MLPA and aCGH in detecting mosaicism, we studied a de novo mosaic ring chromosome 22 in a 5-year-old girl diagnosed with autism. Banding analyses revealed a karyotype mos 46,XX[58]/46,XX,r(22)(p12q13.3)[42]. FISH analysis using commercially available probes for subtelomere 22qter and all telomeres showed a terminal deletion in the ring chromosome. Further characterization of the r(22) by aCGH using Agilent SurePrintG3 Microarray 4x180K narrowed down the deletion to the distal band 22q13.3, 0.84 Mb in size. In total, 34 genes were deleted, including all genes distal from ALG12. Subsequent MLPA analysis showed a discrepancy between different kits. Two subtelomere-kits (P036 and P070) did not detect the deletion, but the Microdeletion syndrome-1-kit (P245) clearly revealed deletion of SHANK3-gene. However, Autism-1-kit (P343) only revealed decreased values for probes targeting SHANK3-gene. Here, we could show that MLPA is less sensitive in detecting mosaicism than aCGH. Difficulties in the interpretation of certain MLPA probe sets are probably due to the probes present in the corresponding kits. Consequently, this can affect the diagnostic potential of MLPA technique in general and especially for detection of mosaic cases.
Background: Achondroplasia and hypochondroplasia are autosomal dominant skeletal dysplasias, which usually occur as a result of de novo mutations in the gene for fibroblast growth factor receptor 3 (FGFR3). The mutations lead to excessive inhibition of bone growth of the limbs. While the diagnosis of achondroplasia is based on characteristic clinical and radiologic findings, diagnostic criteria for hypochondroplasia are less reliable due to miscellaneous clinical presentation and the lack of characteristic radiologic features. Molecular testing is the final confirmation of clinical diagnosis. More than 99% of individuals with achondroplasia have p.G380R mutations (c.G1138A and c.G1138C) in FGFR3 gene and p.N540K mutations (c.C1620A and c.C1620G) represent about 65% of all pathologic alleles in hypochondroplasia.

Methods and results: Here we present the analysis of mutations in FGFR3 gene in a group of 54 patients evaluated in the Zagreb Children’s Hospital and suspected of having achondroplasia or hypochondroplasia/mild form of skeletal dysplasia with disproportionate limbs using PCR/RFLP method and/or sequence analysis of select exons. In all patients with achondroplasia, p.G380R mutations were detected. p.N540K mutations were found in one-third of patients with hypochondroplasia/mild forms of skeletal dysplasia with disproportionate limbs. In one subject with hypochondroplasia, we identified a new mutation p.I376N in transmembrane region of the gene.

Conclusion: In early infancy, it is sometimes difficult to make unfailing clinical diagnosis of the exact type of skeletal dysplasia, especially when patients have atypical/mild clinical/radiologic manifestations of disease. Genetic testing of the FGFR3 gene will establish the diagnosis in a significant number of patients and represents a valuable aid in timely diagnosis and genetic counseling of affected families.
DIFFICULTIES IN REGISTERING SYNDROMIC DISORDERS

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Introduction: Registries of rare diseases have been established in many countries at the national and local levels in order to collect knowledge for research, management and treatment of rare diseases. Congenital anomalies (chromosomal disorders, syndromes, associations) represent a substantial group among all rare diseases, mostly covered by EUROCAT. Some of them are extremely rare, and therefore the necessity for global registry of them is even more important. However, in daily routine, many obstacles in the registration of rare syndromic disorders appear. This arises from many factors, e.g., difficulties in detecting the proper syndrome; variables in the appearance, specificity and sensitivity of every dysmorphic sign; expensive diagnostic procedures; and novel genetic discoveries that can change the group to which a certain syndrome has been classified.

Materials and methods: A registry of chromosomal and syndromic disorders has been established at our hospital. A group of 420 patients were evaluated, divided into twelve groups according to modified classification from Gorlin’s textbook of syndromes. A system of registration of confirmed as well as unsolved cases has been developed. For unsolved cases, communication with expert organizations was established. If there was no diagnosis established, these cases were collected in a separate folder. For every child with rare disease, a special identity card has been designed. Differential diagnosis was added in the card using London Dysmorphology Database.

Discussion: The diagnosis of a specific dysmorphic syndrome is the state-of-the-art for clinical recognition, which includes collecting, sorting and combining the set of minor and major anomalies in a recognizable pattern. Examples of the difficulties in registering a specific syndrome will be shown. The registry of rare syndromes is the first step for providing the mechanism of communication with specialists from other countries; establishing their molecular background; and raising awareness of medical personnel and public institutions of their specific needs.
Preconceptional and prenatal care

P31
THE FOLIC ACID INTAKE PATTERN BEFORE AND DURING PREGNANCY IN A SAUDI POPULATION

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Although the role of folic acid (FA) in the prevention of neural tube defects (NTD) is well documented in the literature, its optimal use is still low in most countries. The aim was to study the pattern of FA intake in Saudi women who received their obstetric care at the Prince Sultan Military Medical City Hospital, Riyadh, Saudi Arabia. This was a case-control study nested within a 3-year cohort project to study the pattern of birth defects. Demographic data including FA use were collected. The mothers were classified as group 1 (FA taken before and during pregnancy), group 2 (FA taken during pregnancy), group 3 (no FA intake) and group 4 women (who could not remember taking FA or were not sure). The study included 1530 mothers, 785 mothers of babies with birth defects and 745 mothers selected as controls. The distribution of women according to their FA use is shown in Table 1. There were 25 cases of NTD: 1 in maternal group 1; 21 in group 2 and 3 in group 3. Family income and level of education were found to have favorable effect on appropriate FA intake. Other maternal demographic characteristics will be presented. Optimal FA intake was found to be low in this Saudi population, highlighting the need of health education and adequate staple food fortification.

Table.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of women</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>177</td>
<td>11.6</td>
</tr>
<tr>
<td>Group 2</td>
<td>1209</td>
<td>79</td>
</tr>
<tr>
<td>Group 3</td>
<td>104</td>
<td>6.8</td>
</tr>
<tr>
<td>Group 4</td>
<td>40</td>
<td>2.6</td>
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</tbody>
</table>
Iron is mandatory for normal fetal development. Iron deficiency anemia during pregnancy is a risk factor for preterm delivery and low birth weight. An adequate iron balance during pregnancy implies body iron reserve of ≥500 mg at conception (50 μg/L). The physiological iron requirements during gestation cannot be fulfilled solely through dietary iron. Iron supplements during gestation consistently increase serum ferritin and hemoglobin and reduce the prevalence of iron deficiency anemia. We analyzed ferritin in women with spontaneous abortion before the next pregnancy. We analyzed data from the Genetic Counseling Unit, Split University Hospital Center, for the 1985-2010 period. Data on serum Fe and ferritin levels were available for only 121 of 568 women. Of these 121, only 13 women had low serum Fe level, but 93 (76%) had ferritin level lower than 50 μg/L (suggested guideline ≥500 mg at conception or 50 μg/L); 21% had ferritin lower than 10 μg/L; 13% had ferritin 10-14 μg/L; and 42% had ferritin 14-50 μg/L. Chronic infection (urogenital) can lead to iron deficiency. Fe starvation promotes degradation battery of Fe-dependent metabolism and Fe storage. In the same period, we collected data on 451 couples. Chromosomal analysis and analysis of spontaneous abortion material showed a higher number of de novo chromosomal changes in aborted material (trisomy, tryploidy, etc.), then in their peripheral blood samples. It is important to prevent iron deficiency in pregnant women. Iron supplement should be taken before the next pregnancy to get serum level of ferritin 50 μg/L and 70 μg/L during the first trimester of pregnancy to avoid repeated spontaneous abortions.
The risk estimate for fetal trisomies by first trimester ultrasound and biochemistry is based on calculated cut off values to achieve a high detection and low false-positive rate. In the wake of uprising patient autonomy, it was proposed to replace these cut off s completely by patient feelings. The aim of this study was to test our hypothesis that test sensitivity and specificity would be destroyed by replacing cut off s by patient feelings. This retrospective study investigated the performance of first trimester screening for trisomies using data of all hospital based combined tests in Styria between 2003 and 2009, combining it with data of the Styrian Malformation Registry where all fetuses or neonates with trisomy 13, 18 or 21 were registered. Detection rate in 8,739 combined tests and 53 fetuses with trisomy 13, 18 or 21 was analyzed in two ways: by the traditional Fetal Medicine Foundation (FMF) 1:300 cut off , or by ‘patient feelings’ in terms of judging the background-to-adjusted-risk difference (delta method) using decision lines from minus 10% to minus 50%. The traditional use of a cut off of 1:300 resulted in 7.4% test false positives (644/8739) and a 71.7% detection rate (38/53). A 50% delta decision line would result in 5.5% false positives (482/8739) and 64.0% detection rate (34/53). The strength of the combined test using the FMF cut off strategy is well known. If a different strategy to interpret the test results is used, only large delta changes between background and adjusted risk would influence the detection rate, which means that various delta decision lines changed only marginally the diagnostic value of the combined test.
USE OF QUANTITATIVE FLUORESCENT POLYMERASE CHAIN REACTION AND FLUORESCENT IN SITU HYBRIDIZATION FOR RAPID DETECTION OF ANEUPLOIDIES ON UNCULTURED AMNIOCYTES AT ZAGREB UNIVERSITY HOSPITAL CENTER

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Numerical and unbalanced structural chromosome abnormalities are the main cause of developmental disabilities and congenital malformations in man. The majority of chromosome abnormalities identified in prenatal samples are trisomy for chromosomes 13, 18 or 21 and sex chromosome aneuploidies. Karyotyping is the ‘gold standard’ in prenatal diagnosis, but the period of 10 to 20 days for obtaining results led to the introduction of quantitative fluorescent polymerase chain reaction (QF-PCR) and fluorescent in situ hybridization (FISH) tests for rapid detection of common chromosome aneuploidies on uncultured amniocytes within 1-2 days. The most widespread prenatal application of FISH is based on using three centromeric probes for chromosomes 18, X and Y and two locus-specific probes for chromosomes 13 and 21. On the other hand, QF-PCR for the molecular diagnosis of aneuploidies requires PCR amplification of several polymorphic markers for each chromosome tested. Although fast and reliable, both methods deal with problems such as mother cell contamination and mosaicism, which are hard to detect and can modify results. QF-PCR enables analysis of many samples at once, while FISH remains expensive, but more precise in detection of mosaicism. We tested 2,072 samples for trisomies 13, 18, 21 and sex chromosome aneuploidies using QF-PCR in the past nine years and 463 samples using FISH in the past four years. Abnormalities were detected in 53 of QF-PCR and 20 of FISH samples and all of them were confirmed by karyotyping. The QF-PCR and FISH methods, as prenatal screening of aneuploidies, are valid for detecting the first evidence of chromosome abnormalities in the second trimester of pregnancy. However, for complete numerical and structural chromosome analysis of all chromosomes, conventional karyotyping still plays a key role. Namely, QF-PCR and FISH methods are unable to detect aneuploidies of those chromosomes not included in this screening and their structural changes.
Spontaneous abortion is one of the most common complications of pregnancy, caused by exogenous factors, infections and chromosomal abnormalities. Here we present results obtained from data collected at Genetic Counseling Unit (GCU), Split University Hospital Center for the 1985-2010 period on couples with recurrent pregnancy loss. There was a higher number of de novo chromosomal changes in aborted material from those who had normal constitutional karyotype and of urogenital infections among those who had balanced chromosomal translocations. More than 1000 married couples attended GCU for recurrent pregnancy loss. We included 451 couples with repeated or habitual abortions; ‘maternal age effect’ was not present, but male partners of the women who had experienced three miscarriages were slightly older. Siblings in the second generation of women and men had a higher number of spontaneous abortions than the general population. Both men and women had significant statistical correlation with previous urinary and/or genital infections. Exogenous factors included smoking, computer working, food and chemicals for women, while in men exposure to heat, cold and alcohol predominated. We found carriers of balanced translocation in only 1.8% and mosaicism in 13 women and 2 men. Samples from aborted material had somatic chromosome trisomy and triploidy. Cytogenetic evidence of the causes of recurrent miscarriages was obtained for couples with balanced chromosomal translocation and we could recommend preimplantation diagnosis before the next pregnancy. At GCU, relevant information can be provided by taking careful and detailed history data and drawing family trees. This constitutes an important framework for further procedures to explain the causes of complex multifactorial process such as recurrent miscarriages.
The Basque Country takes part in the European network for congenital anomalies surveillance since 1990. The number of Down syndrome (DS) cases has increased since 1990 with amniocentesis offered to women aged >35, but cases diagnosed prenatally accounted for 75%. In 2006, an assessment was carried out in order to recommend the best screening strategy for the Region. In 2008, the Basque Parliament approved the screening test for every pregnant woman through biochemical and ultrasound markers in the first trimester. In positive cases, a CVS/amniocentesis and termination of pregnancy is offered depending on the result. After a pilot project in 2009, the Program was fully implemented in 2010 and offered in the Public Health Service free as a new test in the pregnancy surveillance protocol. The coordinated work and quality control of the process and results are the keys of the Program. Midwives explain the screening and manage cross-referral to biochemists and ultrasonography. Biochemists, gynecologists, geneticists and epidemiologists are involved to check and adjust the processes. Web software connected with clinical databases has been developed to allow the network utilization. Main results: on 31/12/2012, 53,261 women had undergone screening, mean age 33.2 (SD 4.68). Detection rate for DS was 88.6% (CI 95% 83.9-93.2).
PREGNANT WOMEN’S ATTITUDE TOWARDS PERICONCEPTION FOLIC ACID INTAKE

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Background: In periconception care, there is a need to pay attention to optimal folic acid supplementation for preventing congenital anomalies and complications associated with childbirth, which in many cases does not happen. The objective of this study was to determine the relationship between preconception folic acid supplementation and socioeconomic and health behavioral factors among pregnant women.

Study design: Since 2008, a population-based monitoring system has been established in 20 districts of health visitors. In the cohort study, data collection was continuous. We analyzed 1,035 questionnaires with multivariate logistic regression. Our explanatory variables were smoking, alcohol consumption habits, vitamin and dietary supplement consumption, employment, self-assessment of health, socioeconomic status, place of residence, age, education and preparation for pregnancy. We used odds ratios (OR) and 95% confidence intervals (95%CI) to represent the results.

Results: In the preconception period, 49% of pregnant women received folic acid. The supplementation was more frequent (61%) in those who were prepared for pregnancy, while in women who were not prepared the rate of supplementation was only 23%. This difference was significant (p<0.001). The logistic regression model revealed the lack of preparation for pregnancy (OR=0.46; 95%CI=0.32-0.66) and lack of vitamin product consumption before pregnancy (OR=0.24; 95%CI=0.17-0.36) to be significant negative predictors. However, the high level of education (OR=5.37; 95%CI=2.25-12.80) and high socioeconomic status (OR=2.27; 95%CI=1.27-4.05) significantly increased the odds of folic acid supplementation.

Conclusion: It is estimated that 70% of neural tube defects can be prevented by adequate folate levels. The national nutrition survey concluded that the average intake of folic acid from food does not cover the amount needed. Intervention programs should be promoted to increase folic acid intake. Our results will be useful in identifying the target population, particularly women who are not prepared for pregnancy and have a low socioeconomic status.
Public health policies and health care for children with congenital anomalies

P38
RADIOLOGIC IMAGING IN CHIARI TYPE I MALFORMATION – DIAGNOSING THE DISEASE, ASSOCIATED CONDITIONS AND COMPLICATIONS

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Chiari type I malformation or cerebellar tonsil ectopia is a condition defined as caudal protrusion of ‘peg shaped’ cerebellar tonsils below foramen magnum for more than 5 mm, caused by a mismatch between posterior fossa size and cerebellum. The causes of this malformation can be found in embryonic development with underdeveloped occipital enchondrium or genetic influences that include syndromic/familial midline anomalies and specific gene mutation. The condition is present in 0.01% of the population with the male to female ratio of 1:1.3 and is often associated with craniocervical junction bony anomalies, platybasia, as well as with other syndromes like Klippel-Feil or conditions such as neurofibromatosis type I. Up to 50% of the patients are asymptomatic, but the condition may cause a variety of symptoms grading from mild (hiccups, headaches) to more severe resulting from brainstem compression, syringohydromyelia or hydrocephalus. As symptoms can be completely absent or mild, the diagnosis may be set in different life periods varying from early infancy to adulthood. We present a case of a 6-year-old girl with Chiari type I malformation, with special emphasis on imaging modalities. Although thorough patient history and physical examination are always a cornerstone of proper diagnostic procedure, it is necessary to top them with appropriate imaging modalities. Magnetic resonance imaging (MRI) is the best imaging tool with thin sagittal views of craniocervical junction used for setting a diagnosis of cerebellar ectopia. MRI is also used to differentiate genuine malformation from potential secondary causes of cerebellar tonsil herniation and to detect associated conditions or complications. Conventional radiography and computed tomography are used to visualize and describe underlying bony malformations, while other diagnostic tools such as ultrasonographic and nuclear medicine findings can be a good way of appraising disorders of cerebrospinal fluid and influences of potential treatment.
The Hungarian Congenital Abnormality Registry (HCAR) was established after the greatest tragedy of human teratology, the thalidomide-Contergan catastrophe in 1962. It could be one of the first national-based registry in the world based on the mandatory notification of patients with different structural birth defects, i.e. congenital abnormalities (CAs) by medical doctors. The major goals of the HCAR were to determine the baseline total prevalence of specified CAs, to detect temporal and spatial clusters of CA (such as increase of isolated transverse type of congenital limb reduction (CLR) between 1975-1978 and detection of an extreme spatial cluster of different CAs in 1991 in small Hungarian village). In addition some other increased trends were observed such as hypospadias and Down syndrome. The Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) was established in 1980. The main objective of this system was the evaluation of the teratogenic potential of different drugs; maternal diseases and potential environmental and occupational hazards. Until now, 183 substances have been evaluated in this case-control system. The major finding was that the possible teratogenic effect of drugs is exaggerated while the benefits of necessary drug treatments are neglected (e.g. antifever drugs can prevent the teratogenic effect of high fever related maternal diseases). Our main research project in the last 10 years was connected with the systematic analysis of possible association of all maternal diseases during pregnancy with the risk of CAs, preterm birth and low birth weight. In the frame of EUROCAT Joint Action 2011-2013 specific public health indicators for CA, such as perinatal mortality, prenatal detection rates and termination of pregnancies due to severe CA, Down syndrome live birth prevalence were provided. Here some important results of HCAR between 1962 and 2011, i.e. during 50 years are reported.
CONGENITAL ANOMALIES DURING A FIFTEEN-YEAR PERIOD AT UNIVERSITY DEPARTMENT OF PEDIATRICS, DEPARTMENT OF MEDICAL GENETICS, SPLIT UNIVERSITY HOSPITAL CENTER, SPLIT, CROATIA

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Aim: This report shows the frequency of genetic illnesses at Department of Medical Genetics, University Department of Pediatrics, Split University Hospital Center, from 1995 till 2010, and emphasize the importance of the respective workup.

Methods: A total of 1293 patients were examined, 528 of them children or adult patients with gene disorders, chromosomal or malformation syndromes, 59% with reproductive problems and 58% with chromosomal changes.

Results: Patients with gene disorders were examined in 27% of cases and 38% of the samples were sent abroad. For every patient with chromosomal and microdeletion syndromes, we could give genetic information and offer prenatal diagnosis (118 by karyotyping and 55% by FISH). Genetic mutation was not found in everyone (of 61 patients), so complete genetic diagnosis was available only in a small proportion of patients. The prevalence of patients with genetic changes in one year was expressed as percentage of the number of hospitalizations at University Department of Pediatrics for genetic condition during the year. During one year, 9% of patients with genetic malformations and disorders were treated out of Department of Medical Genetics at other departments of our University Department of Pediatrics.

Conclusion: It is important to emphasize the purpose of genetic testing, which opens the possibility of providing genetic information to the families and of using various methods of prenatal diagnosis in specific cases.
Background: Complications of people living with disabilities are growing connected to access and orientation in public buildings. This phenomenon is caused by improved life expectancy in children affected by genetic disorders, improved efficiency in care of premature babies and patients with rare diseases, and growing number of adult patients with chronic diseases.

Objective: Our aim was to develop tools with which we could estimate the accessibility to public buildings. The developed instrument system was tested in a Hungarian sample and the results were compared with a parallel study that was performed in Romania. A secondary aim was to compare access to public buildings in Hungary and Romania.

Methods: A cross-sectional study was performed in Hajdu-Bihar County in Hungary and in Satu Mare County (Romania). Through a multi-step sample selection (settlement type and type of buildings), the sample was stratified to be representative in the two counties, which allowed comparison between the two countries. Thirty-seven Hungarian and 39 Romanian buildings were chosen. Statistical analysis was performed with Fisher exact test using Stata 9.2; the level of statistical significance was set at p<0.05.

Results: Appropriate wide pavement was found in close environment of 72.97% of Hungarian buildings and 92.31% of Romanian buildings (p=0.034). In Hajdu-Bihar County 54.05% and in Satu Mare County 63.16% of public buildings had barrier-free access, yielding a nonsignificant difference (p=0.423). In Hungary, significantly more toilets for people with wheelchair were found than in Romania (37.84% vs. 15.79% of investigated buildings; p=0.028).

Conclusion: Overall, in the majority of buildings in both countries, the construction and conversions are not appropriate. In Hungary, the right for equal opportunities of disabled people is not respected, especially Act § 7/ XXVI./ 1998, in which equal access to public services for people with disabilities is ensured.
NEUROSURGICAL TREATMENT OF CONGENITAL ANOMALIES OF THE CENTRAL NERVOUS SYSTEM – TEN-YEAR EXPERIENCE AT ZAGREB UNIVERSITY CHILDREN'S HOSPITAL


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Congenital anomalies of the central nervous system are among the most common entities in clinical practice of pediatric neurosurgeon, but the minority of them require neurosurgical operation. At Zagreb University Children’s Hospital, in the last 10 years we treated various congenital malformations, including brain malformations (arachnoid cysts, neurenteric cysts, hamartomas, Chiari, congenital hydrocephalus, Dandy Walker cysts, corpus callosum anomalies, schizencephaly, polymicrogyria, vascular malformations of arteriovenous and venous types, pineal cysts, encephalocoeles), spinal cord malformations (spina bifida, diastematomyelia, meningocoele, myelomeningocele, tethered cord, tight filum terminale, syringomyelia), skull and spine bone malformations (platybasia, basilar invagination, atlas agenesis, Klippel Feil anomaly), and other symptomatic or incidental findings. The majority of patients were included in team workup, and all diagnostic and clinical investigations were performed. Less than 15% of all patients required neurosurgical operation, and the majority of patients were followed up on the outpatient basis for years, without deterioration in their neurologic or mental status. In our work, we have realized that it is very important to distinguish real congenital malformation from various anatomical variations that are normal findings, especially for neurovascular congenital pathology. In this presentation, we describe the indications for neurosurgical treatment, analyze the most common types of brain and spinal cord malformations seen in our practice, and present diagnostic workup and operative images for the most common entities treated microsurgically in the last ten years at our hospital.
Ritscher-Schinzel or 3C syndrome is a rare, autosomal recessive syndrome characterized by craniofacial, cerebellar and cardiac anomalies. The criteria to establish this syndrome are the presence of cardiac malformation other than isolated patent ductus arteriosus, cerebellar malformation and cleft palate or ocular coloboma, or four of the following seven findings: prominent forehead, prominent occiput, hypertelorism, down-slanting palpebral fissures, low-set ears, depressed nasal bridge and micrognathia. This is a case report of a female infant delivered by cesarean section after 38 weeks of gestation (birth weight 3,650 g, birth length 48 cm, Apgar score 8,8) by a healthy 29-year-old mother. There was no history of parental consanguinity, her father and sister are healthy. In the 20th week of gestation, Dandy-Walker malformation was suspected and confirmed by postnatal head ultrasonography that showed enlarged cisterna magna and cerebellar vermis hypoplasia. Karyotype was 46, XX. At birth, she had multiple craniofacial abnormalities including low-set ears, depressed nasal bridge, hypertelorism, down-slanting palpebral fissures, and micrognathia with protruding tongue. Echocardiography showed atrial septal defect and dysplastic pulmonary valve. According to these specific cerebellar, cardiac and facial malformations, this is the youngest patient with 3C syndrome diagnosed in newborn age. From the first days of life, she had problems with feeding. She did not tolerate any food and was continuously fed by a nasogastric tube. Contrast examination of gastrointestinal tract showed anomalies of intestinal rotation and fixation. Due to failure to thrive at the age of 3.5 months (birth weight 3,850 g, <5th percentile), surgical treatment (adhesiolysis) was performed, however, without significant improvement. At the age of 5.5 months, she was hypotonic, still fed by nasogastric tube, weight 4,390 g (<5th percentile).
EPIDEMIOLOGICAL CHARACTERISTICS OF NEURAL TUBE DEFECTS IN HUNGARY

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Background: Children born with neural tube defects (NTDs) such as spina bifida now survive well into adulthood owing to development in medical technology, which has led to increased life expectancy. Therefore, it has become a major priority to follow these patients and their care in the health care system. There is a unique possibility of using discharge database to study epidemiological characteristics of rare diseases. We can conclude on the quality of health care and the structure of health care systems.

Methods: We used outpatient and inpatient discharge database of the Hungarian Health Insurance Fund, which covers total Hungarian population and all diseases, and includes data in connection with health care from 2004 to 2006. We studied all patients registered with the Q00-Q01-Q05 ICD code.

Results: The database registered 341 inpatients in the 2004-2006 period (43.1% male and 56.6% female). The total prevalence of NTDs in Hungary between 2004 and 2006 was 0.33/10,000. Sixty institutes provided services for all patients but only 3 served nearly half of all patients (49%). The concentration of episodes (number of service/patient) was observed, with 2 hospitals being responsible for 52% of all services. The correlation between the number of cases and number of episodes per patient was significant (p=0.003), thus, increasing the number of patients by institutes would be associated with increasing frequency of treatment. A patient received service 1.88 times/3 years in Hungary, but there was regional variation (minimum: 1.14 episodes per patient; maximum: 2.29 episodes per patient). Patients travelled more than 100 km in 31% of cases to get care.

Conclusion: The discharge database could be used to publish data concerning health care service, which will facilitate planning and decision-making in association with health care. It can also be used in comprehensive studies of NTDs by following the patients born with the disease, and characterizing health care quality indicators among them.
Neonates with Cleft Lip and/or Cleft Palate born in Pula General Hospital during a Ten-Year Period – An Overview

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Cleft lip and cleft palate are caused by abnormal facial development during gestation. Also, they can occur together as cleft lip and palate. Approximately 1 in 700 neonates have cleft lip and/or cleft palate and can be successfully treated with surgery. The aim is to give an overview of neonates with cleft lip and/or cleft palate born in Pula General Hospital during a ten-year period. We have approximately 1,400 live births per year. In the ten-year period, 18 neonates (12 female and 6 male) were admitted to our Neonatology Department. Half of them were born by spontaneous delivery and the other half by cesarean section. One infant was premature (35 weeks of gestation), while others were born at term. Anthropometric measures were normal in all cases except for one; the above mentioned premature infant was hypotrophic (35 weeks of gestation, birth weight 1,690 g). Apgar score was 10 and 10 in first and fifth minute in all cases except for one; one neonate with trisomy 18 necessitated resuscitation, Apgar score was 5 and 8. Four neonates had bilateral cleft lip and palate, seven neonates had unilateral cleft lip and palate, four neonates had cleft palate, and three neonates had cleft lip. Echocardiography, neurosonography and abdominal ultrasound were performed in all cases; seven cardiac defects were found (5 ASD, 1 VSD and 1 Fallot tetralogy) and one renal agenesis. Two neonates were born from uncontrolled pregnancies; one had trisomy 18 and one had renal agenesis and anomalies of extremities – aplastic forearms and thumbs. All the children were fed using special nipples. Craniofacial surgeon was consulted in all cases and several days after hospital discharge all infants were admitted to a tertiary craniofacial center (Dubrava University Hospital, Zagreb) for further diagnostic and therapeutic interventions.
ADVANCING RARE DISEASE RESEARCH: THE USE OF NETWORK OF CONGENITAL ANOMALY REGISTRIES IN THE STUDY OF RARE GENETIC SYNDROMES

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Data on rare genetic syndromes are usually collected in the process of patient care and can be markedly different from population-based epidemiological research data, presenting challenges to their interpretation and reuse for counseling and research purposes. EUROCAT (European Surveillance of Congenital Anomalies) is a network of the population-based registers of congenital anomalies with a common protocol, genetic expertise and data quality review, covering a large population of over 1.5 million annual births across Europe. This provides an opportunity to analyze very rare diseases that lack reliable epidemiological data on the prevalence, possible causes, clinical manifestations, natural course, survival, treatment and care. In this study, we analyzed patients with five rare genetic syndromes: oculoauriculovertebral spectrum, Beckwith Wiedeman, Treacher Collins, Meckel Gruber, and Holt Oram, recorded in the 1990-2009 period in 34 population-based registries from 16 countries. We present data on the prevalence of all birth outcomes, associated congenital anomalies, prenatal diagnosis, survival and other epidemiological and clinical characteristics of these conditions. The collected data further expand perspective obtained from hospital-based datasets and can be used for counseling, evaluation of quality and outcome of diagnostic practices and treatment, and for further research that will advance scientific knowledge and improve patient care in these rare conditions.
HEALTH CARE FOR CHILDREN WITH CONGENITAL ANOMALIES – TRACHEOSTOMY AS A WAY OF LONG-TERM AIRWAY MANAGEMENT

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Tracheostomies are increasingly performed in pediatric population in the context of long-term treatment. In our patients with genetic disorders, it is usually done for one of the three reasons: profound hypotonia, to bypass an obstructed upper airway and to clean the airway, and usually for safer oxygen delivery to the lungs. We report on three patients with tracheostomy. In a 7-year-old boy who probably suffered from a rare form of mitochondrial disease with profound hypotonia and myoclonic epilepsy, endotracheal tube insertion was performed at the age of 19 months. He had a tracheal cannula for the last 5 years. In a 3-year-old girl with Marshall-Smith syndrome, endotracheal tube insertion was performed at the age of 2 weeks. Marshall-Smith syndrome is a rare disorder characterized by accelerated skeletal maturation, dysmorphic facial features, microrretrognatia, profound hypotonia, failure to thrive, and associated with mental retardation of variable degree. She had a tracheal cannula for the last 3 years. A 6-year-old girl with translocation form of trisomy 13 had typical clinical features including cleft palate, cardiac anomalies, microcephaly, developmental delay, microophthalmia, seizures, frequent apnea, and skeletal anomalies. Because of frequent complicated pneumonia with repeated apnea, she needed mechanical ventilation; tracheostomy was done at the age of 5.5 years. She had tracheal cannula for the last 9 months. Parents of the children with tracheal cannula inserted due to genetic disorders at our department have been fully trained to manage the children at home including airway management and resuscitation. Health insurance covers all equipment for the child with tracheostomy, and parents exchange information through the association of children with tracheostomy. We already have a good long-term positive experience in monitoring children with congenital anomalies and tracheotomy, which provides a good quality of life and care in their own families.
A TOOLKIT TO ASSESS HEALTH NEEDS FOR CONGENITAL ANOMALIES IN LOW- AND MIDDLE-INCOME COUNTRIES: AN INSTRUMENT FOR PUBLIC HEALTH ACTION

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Congenital anomalies are responsible for an increasing proportion of childhood morbidity and mortality, particularly in low- and middle-income countries. In response to a call from the World Health Assembly in 2010 to tackle congenital anomalies as a public health priority, the PHG Foundation has undertaken a collaborative program providing the "international technical guidance" through the development of a web-accessible 'Toolkit' (http://toolkit.phgfoundation.org), which delivers a step-wise guide based on the principles of health needs assessment as a prerequisite for strategic planning to develop regional and national programs to tackle congenital anomalies. In this presentation, we will highlight how the Toolkit has been used in Argentina, Brazil, Uruguay, and India to highlight the need for public health action in the area of neural tube defects (NTD). In both Argentina and Brazil, following the health needs assessment, several needs were identified including improved registration of NTD cases, and public and professional education. Use of the Toolkit in Argentina helped highlight major differences between the two provinces studied. In Brazil, findings suggest that the current levels of folic acid fortification may be suboptimal. In Uruguay, health needs assessment of the newborn screening program highlighted the need for a standardized protocol for newborn physical examination and the requirement of an epidemiological surveillance program linked to the newborn screening program. In India, we have started by quantifying the burden of NTDs in terms of birth prevalence. All these examples highlight not only the flexibility of the way in which the Toolkit can be used but also how the Toolkit can bring together people working on the same issue, and can engage and motivate both experts and stakeholders to work together to tackle the problem of congenital anomalies.
BACKGROUND: Congenital malformations have public health significance because they are the second most common cause of infant death. Neural tube defects (NTDs) are one of the most common birth defects, their prevalence in Europe was 0.24/10,000 among live born babies in 2008. Because of the problems associated with NTDs, affected people require medical attention for life; this is a huge burden not only upon families but upon the society too. Our study objectives were to describe the cost of treatment for NTDs and to explore the within Hungary geographical differences in financing.

METHODS: Discharge reports of inpatient services were provided by the Pharmaceutical and Healthcare Quality and Organization Development Institute for the whole country. The study period was from 2004 to 2006. Based on the DRG, weight and the national basic fee (€503.45), we determined the cost of care for NTDs.

RESULTS: We identified 341 patients, male 43% and female 57%. The highest number of hospital episodes were observed among children aged 0-2 years; 709 episodes were recorded in NTD patients with a cost of more than €681,356. In Hungary, an average of €1,803 was spent for one person; the highest expenditure for an NTD patient over the 3-year period was recorded in the Central Hungarian Region (€2,258) and lowest in the Central Transdanubian Region (€574).

CONCLUSION: The healthcare cost for people living with NTDs is a major financial burden on the healthcare system. Therefore, prevention of NTD would be humanistic for the individual and financially more beneficial for the society. Development of preconception intervention to promote adequate folic acid supplementation would result in a cost-effective way to reduce the risk of NTDs.
Although rare, the spectrum of fibular hemimelia is the most common lower extremity congenital reduction defect. The incidence of fibular hemimelia is estimated to 1.5 per 100,000 live births, one tibial reduction per 1 million. These reductions could severely affect normal functions of the knee, ankle and foot, and cause significant leg shortening. Surgical treatment is complex, lasting and associated with complications. Our aim is to present clinical outcome in a cohort of patients treated from 1981 to 2006. We collected clinical data and reviewed X-ray appearance of affected limbs. The classification system of Achterman and Kalamchi was used. We noted associated anomalies including upper extremity, femur, knee, ankle and foot. The outcome was related to leg-length discrepancy and foot preservation or amputation. We found 26 patients (28 limbs), 25 with fibular and 3 with tibial reductions in our database. In this study, we evaluated 14 fibular (type IA=3; type IB=3; type II=8) and 2 tibial reductions after skeletal maturity and completion of treatment. According to sex distribution, there were 11 male and 5 female patients (20% bilateral reductions). As associated anomaly, upper extremity reduction was recorded in one patient, femur shortening in 3 patients, and joint anomalies in 5 patients: "ball and socket" ankle joint in 4 and tarsal coalitions in 7 patients; one or more foot lateral rays were missing in 8 patients. Two patients had below-knee amputation. Other patients had preservation of the foot and two cm or less leg-length discrepancy. Our retrospective study and literature review showed that up to 30% of predicted leg-length discrepancy and existence of at least three foot rays were prerequisites for limb reconstruction procedures. Advanced techniques of leg lengthening/foot preservation have changed the approach to lower leg reductions.
Ring chromosome is a structural chromosomal aberration with the incidence of 1:50,000 live borns. It occurs due to terminal deletion on both chromosomal parts, and then fusion of the rest parts into a ring formation. Until now, 70 cases of ring chromosome syndrome have been described in the literature. The diagnosis is often established with delay. Our patient was born from the first pregnancy to healthy nonconsanguineous parents. He was an 11-year-old boy with dysmorphic stigmata noticed directly after birth. He was born at Maternity Ward, Požega General County Hospital, Požega, Croatia. He presented with palatoschisis, hypertelorism, low-set ears, short neck, hypospadia, feet malformation and heart murmur. Fallot pentalogy was diagnosed and operated on. Further cytogenetic analysis indicated the diagnosis of ring chromosome syndrome: 46XY, r (18). In the last 10 years, palatoschisis and feet were operated on. He had multiple respiratory infections and was diagnosed with immunodeficiency A. He walked at 6 years of age, but had psychomotor retardation and short stature. He attended polyvalent, multi-level treatment with speech therapist and psychologist. Although patients with ring chromosome syndrome are mostly diagnosed later in childhood, our patient was diagnosed at an early age, in the first months of life, so treatment was not delayed. However, his development has been significantly impaired and his cognitive functions are much below average.
CLASSIC CONGENITAL ADRENAL HYPERPLASIA DUE TO 21-HYDROXYLASE DEFICIENCY IN CROATIA 1995-2012

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Congenital adrenal hyperplasia (CAH) represents a group of disorders characterized by enzymatic defects in one of the steps in cortisol production. The clinical consequences of CAH are significant and include adrenal insufficiency, genital ambiguity, pseudoprecocious puberty, short stature, and an increased risk of infertility. The aim was to evaluate the incidence, sex, symptoms and age at diagnosis of patients with classic CAH due to 21-hydroxylase deficiency in Croatia born between January 1, 1995 and December 31, 2012. During this 18-year period, 55 classic CAH patients were diagnosed. There were 34 salt-wasting (SW; 23 female:11 male) and 21 simple-virilizing (SV; 10 female:11 male) patients. The mean age at diagnosis was 9 (range: 2-30) days in females and 37 (range: 2-60) days in males with SW form. In SV patients, the mean age at diagnosis was 11 months (range 5 days-13 months) in females and 3.88 years (range 2.5 months-7 years) in males with SV form. The first symptom in all 23 SW females was ambiguous external genitalia, while all 11 males with SW CAH were not diagnosed until development of adrenal crises. All 10 female patients with SV presented with ambiguous genitalia, while all 11 males with SV CAH were not diagnosed until development of adrenal crises. All 10 female patients with SV presented with ambiguous genitalia, while all 11 males with SV CAH presented with signs of precocious puberty. With 796,875 live births and 55 CAH patients born over 18-year period in Croatia, the prevalence of classic CAH was estimated at 1:14,488. The overall male to female ratio found in this study (22:33), as well as the same number of SW and SV (11:11) implies that a significant proportion of males either die unrecognized due to adrenal crises in neonatal period or are diagnosed later in life. Despite improvements in healthcare, our results show that the diagnosis of CAH in Croatia is still delayed and some patients go unrecognized or die, and stress the importance and need for the introduction of a newborn screening program for CAH in Croatia.
SEVERE CONGENITAL LARYNGEAL STENOSIS WITH OTHER MALFORMATIONS

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We present a case of severe laryngeal stenosis at the glottic level with massive ascites and pulmonary hyperplasia in a prematurely born infant with other congenital anomalies. Because of fetal ascites on ultrasonic examination, the mother was admitted to the hospital where an urgent cesarean section was performed because of threatening fetal asphyxia at 33 weeks gestation. Apgar scores were 2/2, the neonatologist tried to intubate the infant, but the attempt was unsuccessful and the neonate expired after 2 hours. At autopsy, male infant weighting 2050 g showed poorly formed ears, distended abdomen and imperforate anus. The abdomen contained ascites, with short small intestine and mobile mesenterium. Both lungs were pale pink and seemed inflated. The larynx could not be probed, the trachea was dilated and filled with transparent mucus. The liver was not divided in two lobes and the quadrate lobe was enlarged. The right kidney was small, irregular cystic spaces were seen on cut surface. Bilaterally the renal pelvis and ureter were dilated. The penile uretra were patent. The rectum ended blindly immediately above the perineum, the large bowel was dilated with meconium. Other organs were unremarkable, except for many petechial haemorrhages on serosal surfaces. The F/P ratio was 9.31. One third of the placental tissue showed gross and microscopic features of old infarction. Serial cuts through the larynx revealed severe stenosis at the glottic level. Microscopically, the lungs were showed features of hyperplasia and the right kidney showed features of multicystic dysplasia. Congenital high airway obstruction (CHAOS) anomalies are rare, of several rare cases described in the literature, some were associated with anomalies of other organ systems. The findings of the placenta cannot be related to malformations of the fetus; they contributed to fetal asphyxia necessitating operative delivery.
Nasal obstruction in neonates is a potentially fatal condition since neonates are obligatory nasal breathers. Congenital choanal atresia results from persistence of the bucconasal membrane, which separates the nasal cavity and the nasopharynx in the early embryonic development. The incidence ranges between 1 per 5,000-10,000 live births, 45% are bilateral, while the right choanae are involved in 71% of unilateral cases. The male to female ratio is approximately 2:1. We present a case report of a female infant born with bilateral choanal atresia at Pula General Hospital. It was the first mother’s pregnancy; during pregnancy, the mother did not use any drugs, did not smoke or take any alcohol, and was not exposed to X-rays. Delivery was performed using a Kiwi vacuum extractor at 41 weeks of gestation. The infant’s birth weight was 3,640 g, birth length 50 cm and head circumference 34 cm. Apgar score was 6/8/9. Respiratory distress and intermittent cyanosis were present soon after birth. Since the clinical condition and oxygen saturation on room air improved when crying, bilateral choanal atresia was suspected. Oropharyngeal airway was inserted to make the airway patent. Since insertion of a feeding tube via the nostril was not possible, an ENT specialist was consulted and confirmed the diagnosis. The infant was transferred to a tertiary care pediatric center (Rijeka University Hospital Center, University Department of Pediatrics, PICU) for further diagnostic and therapeutic management. Oropharyngeal airway was used to make the airway patent during transport. Upon arrival to PICU, an ENT specialist was consulted and computed tomography scan of the choanal region was performed showing membranous bilateral choanal atresia. Endoscopic operation was performed and stents were put in the nostrils. Stents were removed after 11 days. Two days later, the child was discharged from the hospital in good condition and without any signs of respiratory compromise.
ASSOCIATION BETWEEN GROUP B STREPTOCOCCAL SEPTICEMIA AND LATE APPEARANCE OF CONGENITAL DIAPHRAGMATIC HERNIA

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Congenital diaphragmatic hernia (CDH) is a congenital anomaly which consists of a posterolateral defect on the diaphragm, known as Bochdalek’s hernia, and its pathogenesis is not completely understood. Clinical manifestations usually occur during the first few hours of life as dyspnea and cyanosis and it presents as an urgent condition in pediatric surgery and neonatology. However, a few cases CDH (5%-20%) appear after the neonatal period, mostly with nonspecific symptoms. Some authors suggest that ‘late’ or ‘delayed’ presentation of CDH, which is related to group B streptococcal (GBS) infection, may be observed as a different entity. The fact that around 40 cases of CDH related to GBS infection have been reported so far worldwide with unclear pathogenesis and no connection between CDH and other congenital pneumonia, suggests that it seems reasonable to prevent the disease by one of the strategies for prevention of early neonatal GBS infection. We present a case of diaphragmatic hernia associated with GBS septicemia, which appeared in the early neonatal period but was recognized late. In cases of streptococcal sepsis and pneumonia in newborns with prolonged recovery or sudden respiratory dysfunction, consideration and search for the possible late presenting congenital diaphragmatic hernia may be lifesaving.
DYSCEPHALY AND BIRD-LIKE FACE-HALLERMANN STREIFF SYNDROME: CASE REPORT

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Hallermann-Streiff syndrome (HSS) is a rare disorder characterized primarily by head, face and dental abnormalities. Seven essential signs are used as diagnostic criteria for HSS: dyscephaly and bird-like face, abnormal dentition, hypotrichosis, atrophy of skin, congenital cataracts, microphthalmia, and proportionate dwarfism. In the course of neonatal period and infancy, death may occur due to respiratory challenges secondary to micrognathia and tracheomalacia. We report on a 6-week-old girl born from a third pregnancy (the first two ended in spontaneous abortions) of nonconsanguineous parents, birth weight 3.2 kg. The mother as a newborn had Apgar score 1, breathing problems, failure to thrive with epilepsy, and the same phenotype as the newborn child. The neonate had brachycephalic skull, severe micrognathia, high arched palate, stertorous breathing and inspiratory dyspnea. There were hypertelorism, congenital cataract, epicanthal folds, hypotrichosis of the scalp, and partial syndactyly of the second and third toes on both feet. Neurologically, the newborn presented generalized hypotonia and poor spontaneous movements. Skull radiograph showed hypoplastic mandible and visceral bones. Magnetic resonance imaging showed thin corpus callosum and macrogyria. Echocardiography revealed atrial septal defect. Fiberoptic laryngoscopy showed an omega-shaped epiglottis associated with laryngomalacia. Chromosome analysis was normal. The baby was not able to suck the breast or bottle, and had to be fed via an orogastric tube for first two months of life. Now the child has 18 months, delayed psychomotor development, cataract is spontaneously regressed, and atrial septal defect has been occluded. She is often treated at the hospital for respiratory infections. HSS is a rare genetic condition that occurs sporadically and is not associated with chromosomal anomalies. There is no cure for HSS; the affected individuals need a team of specialized doctors for treating the various problems, which can occur. Mutations in GJA1 gene have been associated with oculodentodigital dysplasia, heart malformations and HSS.
Partial urorectal septum malformation sequence (pURSMS) (or ‘persistent cloaca’) is a rare congenital anomaly characterised by a joining of the urethral, anal, and genital openings into a single common channel. This large population-based study describes the prevalence, additional anomalies, pregnancy outcomes, and infant survival, of pURSMS in England and Wales. All cases of pURSMS notified to seven congenital anomaly registers in England and Wales (all part of the British Isles Network of Congenital Anomaly Registers) during 1985-2010, whether delivered as live births, spontaneous fetal deaths (≥20 weeks gestation), or elective terminations of pregnancy for fetal anomaly (TOPFA; any gestation), formed this population-based case series. Risks of spontaneous fetal and infant death were examined by the Kaplan-Meier method. Differences in prevalence over time, and between regions, were examined by multilevel Poisson regression. 117 cases were recorded among 4,251,241 total births. 58 (50%) were delivered as live births, six (5%) as spontaneous fetal deaths, and 53 (45%) as TOPFA. The total prevalence was 2.8 (95% CI: 2.3-3.4) per 100,000 total births, increasing significantly over time (p=0.002) and differing significantly between regions (p=0.005). 111 (95%) cases occurred in singleton pregnancies and six (5%) in separate twin pregnancies. Fetal sex was known for 109 cases of which 79 (71%) were female and 30 (29%) were male. 77 cases (66%) had at least one additional major structural congenital anomaly outside the perineum, including 67 (57%) with renal, 29 (25%) with musculoskeletal, 26 (23%) with digestive system, and 24 (21%) with cardiovascular anomalies. The risks of spontaneous fetal and infant death were estimated as 8.9% (95% CI: 4.1-18.8) and 26.3% (95% CI: 15.1-43.4) respectively. This is the largest study of the epidemiology of pURSMS. This information should be valuable for families and health professionals whenever a case of pURSMS is diagnosed.