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Epidemiology of Congenital Malformations

Etiology of Congenital Malformations

Prevention of Congenital Malformations and Prenatal Diagnosis

Report on a Cluster of Trisomy 21 Cases in the Region of Rheinhessen, Germany in 2004

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Introduction

At a prevalence rate of approximately 1:500, trisomy 21 (Tri21) is the most important genetic cause of mental retardation. Environmental factors may play a role and exert a deleterious effect during meiosis II, a sensitive period shortly after conception.

Subjects and methods

The population-based Birth Registry Mainz Model actively surveys Rheinhessen, a region of approximatly 400,000 inhabitants. Since 1990, a total of 48,303 newborns have been screened, covering about 90% of all birth in this area. Statistical analysis was performed with 2x2 tables assuming a Poisson distribution.

Results

Between January and June 2004, 8 live births with Tri21 were observed, which exceeds the expected number of about 3-4 live births within a 6-month period. Based on the calculated time of conception of all Tri21 children we found that eleven out of eighteen infants within 2003 were conceived within a period of three months (June to August 2003). From April 1989 until today, a total of 102 newborns and fetuses with Tri21 were recorded, resulting in a ratio of 1:474. A total of 18 cases were documented to be conceived in 2003 (estimated ratio 1:173). The prevalence ratio (RR) for the two periods (1989-2002 vs 2003) is 3.1 (1.9-5.2, $p<0.0001$). Assuming a Poisson distribution of $\lambda = 0.6$, the statistical probability (p) for the occurrence of eleven cases in three months is less than 0.0001.

Discussion

The only proven risk factor for an infant with Tri21 is high maternal age ($\geq$35 years). In 2003 33% of mothers of children with Tri21 were older than 34 years compared to 40% in the preceding years. Smoking, maternal irradiation, alcohol consumption, oral contraceptive, and fertility drug use, as further discussed risk factors were statistical similar distributed between Tri21 cases and the rest of the cohort. Hypotheses include the extreme temperatures (>40°C) between June and August 2003, with very low Rhine and ground-water levels. Planned molecular studies will focus on the origin of the extra chromosome 21 to determine the timing of the non-disjunction event (meiosis I vs II). Case-control studies will evaluate environmental factors (incl. climatic stress).

Congenital Malformations of the Organ of Vision: Epidemiology Data Based on Polish Registry of Congenital Malformations 1997-2001, Diagnostic Recommendations and Genetic Counselling

M Krawczynski and Working Group of PRCM

Introduction

Congenital malformations of visual organ have an increasing contribution to the causes of severe visual handicap in developed countries. In Poland there were no population-based studies on prevalence of congenital eye malformations. The are also no diagnostic recommendations, which refer to early diagnostics of congenital eye malformations (what gives an opportunity of early prevention and treatment, and is the only chance to avoid blindness). There were also no compiled principles of genetic counselling for this specific group of patients. In this connexion, the basic assumption of this study was to fill this gap with possibly complete epidemiological and clinical data with regard to specificity of diagnostic process and counselling

The aims of the Study were
(1) the assessment of prevalence and risk factors of congenital eye malformation as well as the ability of their recognition in neonates and infants before ophthalmologic examination; (2) elaboration of simple methods of visual organ initial examination done by neonatologists and paediatricians, which can make it possible to suspect some congenital pathology of visual organ; (3) elaboration of principles of genetic counselling for particular groups of disorders

Material and Methods
The analysis comprised data from the Polish Registry of Congenital Malformations (PRCM) 1997-2001, including 925,162 consecutive births with 19,200 children identified and noticed because of congenital defects. Among them there were 211 children with 244 malformations of visual organ. The results were statistically analyzed using chi^2 distribution test or Fisher's exact test

Results and Conclusions
(1) These studies have shown that the prevalence of congenital eye malformations is 2.28 for 10,000 births and it locates in lower values of range known from other registries of malformation all around the world. Comparatively low total prevalence of congenital eye malformations, stated in PRCM, with high prevalence of anophthalmos and low prevalence of other congenital eye malformations, suggest that actual scheme of neonate and infant physical examination in Poland is not sufficient to enable early recognition of congenital eye malformation before ophthalmologic examination. (2) Factors that increase risk of occurrence of congenital eye malformations are: female sex (for Q10 and Q11 categories of malformations), birth weight below 2500g, foetal age at birth below 36 weeks, vocational education of fathers and presence of other birth defects (for Q11 category of malformations). (3) It is suggested to complete the scheme of neonates and infants' physical examination by measurement of corneal diameter with transparent ruler and by examination of the eyes with help of pocket medical torch to assess the following traits that can suggest some congenital eye pathology: transparency of cornea; size, shape, colour and reactions of pupils; presence of nystagmus, photophobia, fixed strabismus and oculodigital sign. (4) Significant specificity of congenital malformations of visual organ, frequent risk of loss of vision and imminence with extraocular symptoms, give the reasons for the proposition of detailed principles of genetic counseling with respect to specific needs and expectations of this group of patients.

The Analysis of Factors Influencing High Detection Rate of Congenital Heart Defects in the Podkarpackie Province
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Aim
To analyze the impact of methods of additional detection (screening echocardiography und pulse oximetry), regional stage referral, and watchful follow-up on high detection rate of congenital heart defects in the newborns in Podkarpackie Province.

Patients
Population of patients with congenital heart defects (CHD) enrolled from the cohort of 41832 newly born infants in Podkarpackie Province in years 2002-2003.

Methods
Screening echocardiography and pulse oximetry; specific stage referral system; watchful follow-up.

Results
The total detection of CHD among the newborns in Podkarpackie was 9.6/1000 and the detection of critical CHD was 1.76/1000.

Conclusions
1. The combination of the additional methods of detection, referral and follow-up resulted in highest provincial detection rate of the CHD in newborns registered in Eurocat among Polish population.
2. Diagnostic and organizational algorithm to increase detection of CHD's in newborns is proposed.

Gastroschisis in Wales - Contribution of the Welsh Congenital Anomaly Register (CARIS)
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Background
During the early part of 2004 registry staff expressed anecdotal concern that they had received reports of higher than expected numbers of antenatally detected cases of gastroschisis. These concerns were also expressed by local clinicians. It was agreed that in the first instance CARIS should look at available data to establish the nature and extent of any problem.

Aim
To use routinely available registry data to:

1. Describe the current pattern and recent trends in gastroschisis in Wales
2. To compare levels of gastroschisis in Wales with other parts of the UK and Europe
3. Identify any local clusters
4. Identify potential risk factors or causes

Materials and Methods
CARIS operates a multiple-source reporting system including antenatal and neonatal sources. Relevant information from the database includes:

· Area of residence of mother
· Age of mother
· Estimated date of delivery and date of end of pregnancy
· Maternal smoking, recreational drug use, illness, and prescribed drugs
· When anomaly first detected
· Survival outcome to 1 year of life

Data quality is regularly assessed although, in the absence of a 'gold-standard', analysis of case ascertainment is problematic. Cases of structural anomaly seen on antenatal ultrasound scan are routinely reported. When serious anomalies such as gastroschisis are detected as a local general hospital, the case is usually referred to a tertiary centre for a second opinion. In Wales there are two such centre. Cases from North Wales are referred on to Liverpool Women's Hospital whilst in South Wales referral is made to University Hospital of Wales, Cardiff. To ensure data quality, cases were crosschecked with those known to paediatric surgeons in South Wales. In the absence of direct links to surgeons serving North Wales, obstetricians and paediatricians in North Wales were contacted to see if they knew of any further cases. Numbers of cases and rates of gastroschisis were analysed at All-Wales level for the years 1998-2004. Expected numbers per year were estimated (using Poisson distribution) for each of the 22 local authority areas in Wales and compared to the actual numbers for 2004. Welsh rates were compared to the most recent rates available from EUROCAT. To obtain comparative data for 2003 and 2004, data were requested from other registers within the British Isles Network of Congenital Anomaly Registers (BINOCAR). All cases of gastroschisis known to CARIS were reviewed for possible risk factors. As no population data are available for these risk factors, cases were compared with all other cases of anomaly held by the register.

Results

Case matching with the surgeons for South Wales was complicated by issues of confidentiality. It was difficult to assess case ascertainment for 2004 as cases were being reported simultaneously to both neonatal surgeons and the register. Comparison of live born cases for earlier years suggested that case reporting to the register was complete. The register was initially of aware of one case of gastroschisis that was unknown to the surgeons. Further investigation indicated that this case had small bowel atresia alone and that the diagnosis of gastroschisis had arisen on an inaccurate clinic letter. The diagnosis was therefore removed from the database record. A general increase in cases was detected in Wales for both 2003 and 2004 compared with previous years, although these were not thought to be statistically significant. Live born rate of gastroschisis in Wales for the period 1998-2003 was 4.3 per 10,000 live births. Rates vary between years but were highest in 2003 (6.1 per 10,000 LBs, based on 19 cases). Indications were that numbers for 2004 would equal or be in excess of this figure. [By the end of March 2005 26 live born cases have been confirmed for 2004]. Overall Welsh rates for 1998–2002 were statistically significantly higher than for EUROCAT as a whole. Initial data from other British registers suggested that a non-specific rise in cases in 2003 may have also been seen in other areas of Britain, although further work was required to confirm this. Against this background, a potential cluster of 7 cases was identified in the Bridgend County of South Wales (maximum expected = 3 per year). Unusually, none of the cases were located in the main centre of population but in the old coal mining valleys to the North of Bridgend. A separate investigation in to this potential cluster was undertaken. A statistically significant association with gastroschisis was found for the following risk factors.

· 77% of gastroschisis mothers were found to be under the age of 25 (OR 6.0: 95%CI 4.0 – 9.0).
· Some 10% of mothers had a history of drug abuse (OR 7.4: 95% 3.6 – 15.4)
· Over 60% of mothers were known smokers (OR 4.4: 95% CI 2.9-6.7).

Data to the end of 2002 showed that:

· 86% of all cases were liveborn and of these 94% survived to the end of the first year of life
· the male to female ratio was 1.2 males to 1 female
· Gastroschisis occurred as a single anomaly in 74% of cases.
· Conversely 26% were associated with other anomalies, commonly atrial septal defect or small bowel atresia (6% of cases). 2 cases were associated with chromosomal disorders. Interestingly a further 2 cases of gastroschisis were associated with optic nerve hypoplasia. This rare defect is not often reported, although it to is known to occur more frequently in the babies of younger mothers.
· Antenatal detection was reported in 89% of cases by 24 weeks and rose to 95% by the end of pregnancy

Discussion

Comparison of different data sources suggested that case ascertainment of liveborn cases of gastroschisis by CARIS was complete. CARIS was also able to identify other cases resulting in fetal loss that were (obviously) unknown to the surgeons. There was no way to assess the quality of CARIS data for these cases.

The rise in numbers of cases in Wales from 2003 onwards was greater than might have been expected although, so far, this rise has not been identified as statistically significant. Increases in Wales together with other areas of Great Britain are the subject of ongoing investigation by BINOCAR. Cluster investigation falls outside both the remit and the expertise of the register. At the time that the cluster was first suspected, the process by which further investigation should take place in Wales was not clear. CARIS therefore invited interested parties to a meeting to discuss the

data and agree how this matter might be taken forward. It was decided that Bridgend cases merited further investigation as a potential cluster and a separate investigation into this was undertaken, involving clinical and academic staff from the University Hospital of Wales, the National Public Health Service, Local Authority representatives, the Welsh Assembly Government and CARIS. The Investigation of the cluster of cases in Bridgend County is the subject of a separate report. The aetiology of gastroschisis remains unclear. The risk factors identified from routinely collected CARIS data included maternal age, maternal smoking and drug abuse (although drug abuse was associated with only a small proportion of cases). This supported evidence already published in the medical literature. The association of two cases with optic nerve hypoplasia has not been widely reported in the literature.

Conclusions

· Congenital anomaly registers can play a key role monitoring levels of congenital anomalies and in identifying clusters.
· Routinely collected register data can help the initial stages of a cluster investigation by helping to identify potential associated risk factors.
· Clearer mechanisms need to be put in place in Wales for action to be taken in the event of a possible cluster and its subsequent investigation.
· The quality of CARIS data in terms of case ascertainment for gastroschisis is good.

Increasing Prevalence of Gastroschisis in Europe: A Younger Mother Phenomenon?

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Aim

Gastroschisis is a rare abdominal wall defect commonly associated with young mothers. Recent reports have suggested an increase in prevalence despite a general decrease in the proportion of births to young women in Europe. This study aimed to investigate the increasing prevalence of gastroschisis in Europe, to assess if the increase in prevalence has been restricted to young mothers, and to identify any geographical variation within Europe after taking into account differences in maternal age.

Methods

A population-based analysis of all gastroschisis cases born between 1980 and 2002 was carried out. Twenty-five European regions in 15 countries participated in the study, covering a total of 5.79 million births. Data was extracted from the EUROCAT database which contains standardised comparable data on congenital malformations obtained from a collaborative network of European surveillance registries. All registered cases of gastroschisis that were liveborn, fetal deaths at twenty weeks gestation or more or terminations of pregnancy following prenatal diagnosis of a congenital malformation were included in the study. Cases with a chromosomal anomaly were excluded.

A Bayesian analogue of ridge regression technique was used to calculate estimates of relative risk controlling simultaneously for time, maternal age, and geographical variation. Prevalence rates were standardised to the EUROSTAT 2000 maternal age structure for European births.

Results

In the years 1980-2002 936 cases of gastroschisis were identified, giving an average prevalence rate of 1.62 per 10,000 births. Seventy-four per cent of cases were livebirths, 6% were fetal deaths, and 20% were terminations of pregnancy.

The maternal-age standardised prevalence rose fourfold from 0.34 (95%CI 0.23-0.48) per 10,000 births 1980-84 to 1.33 (95%CI 1.14-1.54) per 10,000 births 2000-2002. Prevalence rose in all age groups, but with steeper trends in the younger age groups. Mothers less than 20 years of age 1995-2002 had a seven-fold risk of gastroschisis compared to 25-29 year olds. Mothers aged 20-24 years were more than twice as likely to have a baby with gastroschisis as mothers 25-29 years.

The unadjusted prevalence rate varied from less than 0.7 per 10,000 births in the three Italian regions to over 3.0 per 10,000 in Mainz and three of the UK regions (Glasgow, Trent, and Wales). Controlling for maternal age, Italy (Campania, Emilia Romagna, and Tuscany) and Southern Portugal showed significantly lower age-adjusted relative risk compared to the average EUROCAT prevalence 1995-2002, varying from 0.36 to 0.60. The highest estimates of relative risk for 1995-2002 were found in Paris (France), Mainz (Germany), Finland, Wales and Trent (UK), varying from 1.7 to 2.3.

Discussion

These findings show that the prevalence of gastroschisis has increased over time in Europe, and that the increase has not just been restricted to younger mothers. There is evidence of geographical variation in risk with some regions having half the average risk and others double the average risk after controlling for maternal age variation. The UK has particularly high rates of gastroschisis especially among the younger mothers.

Conclusion

The environmental factors contributing to the increase in gastroschisis prevalence are not just restricted to mothers under twenty years of age. Geographic variation in risk may provide additional clues to the aetiology of this serious malformation.

Large-Scale Elucidation of Genetic Disease and Implications for Health Care

H Ropers

The human genome is thought to compromise 65-70,000 genes of which 20-25,000 code for protein, but no more than 2,000 of these genes have been linked to specific genetic disorders: thus, the bulk of this work still lies ahead. During the past decade, research in this area has focused on association studies in multifactorial disorders. The outcome of these studies was mostly meagre, which was generally ascribed to too small sample sizes. The alternative possibility, ie. that many of these complex disorders are not really multifactorial but consist of a heterogeneous group of single gene disorders, has received very little attention. It is probably that the role of recessive gene defects and de novo mutations in the aetiology of "idiopathic" disorders, such as sporadic cases with mental retardation and/or multiple congenital anomalies, is much higher than suspected previously, and this could also hold true for disorders that are considered as paradigms for multifactorial disorders, such as congenital heart defects or autism. Taking mental retardation as an example, I will discuss various strategies that have been employed successfully to dissect complex disorders into separate genetic entities and to identify the underlying molecular defects in a systematic fashion. These studies, and the development of novel methods and diagnostic tools, offer great promise for the diagnosis and prevention of genetic diseases, and they may pave the way for treatment of some of them.

Identification of Additional Chromosomal Material with CGH and Fish Techniques in Patients with Phenotypic Abnormalities

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Approximately 30% of small supernumerary marker chromosomes (SMCs) derived from autosomes are related to an abnormal phenotype in their carriers. Because of the varying clinical outcomes attributable to the chromosomal origin of the SMCs, their detailed characterization is of great interest for reliable genetic risk estimation. SMCs may be successfully characterized only with molecular cytogenetic methods. Here we present three phenotypically abnormal patients with marker chromosomes and a case of a de novo chromosomal addition analyzed by FISH, M-FISH and mBAND as well as with CGH techniques. We report a case of three cell lines in which two SMCs derived from chromosome 8 and 21 as well as mar(8) and double mar(21) in a patient with clinical features of trisomy 8p. A patient with mild mental retardation and mar(19) and a case of mar(22) identified in a patient with partial cat - eye syndrome (CES) is also presented. Furthermore, an additional material on chromosome Yp was revealed in a patient with severe mental retardation, hypotonia, microcephaly, short stature and dysmorphic features. Marker chromosomes were identified as der(8)(:p22->q11.2:), der(21)(pter->q21.3) and der(19)(:p11->q13.1). It was also found that additional material on Yp originated from chromosome Xq26->qter. Our results confirm, generally accepted and clinically useful information on the high risk of phenotypic abnormalities in the carriers of marker chromosomes containing euchromatic sequences.

Major Congenital Malformations and 22q11.2 Microdeletions

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Background

Congenital heart defects (CHD) are the most common of all human birth defects occurring in 1% of live births. Previous studies suggest that a number of patients with congenital heart disease have a 22q11.2 deletion syndrome (22q11.2 DS). Orofacial clefts are also among the most common major congenital anomalies and are included in the 22q11.2 clinical spectrum. The clinical phenotype of 22q11.2 DS is highly variable. Patients with mild clinical manifestations and apparently isolated malformation can be easily overlooked.

Objective

To determine should the 22q11.2 deletion analysis become a part of the standardized diagnostic workup for CHD and orofacial clefts

Methods and patients

A consecutive series of one hundred twenty-two patients with two selected major malformations, CHD (64 patients) and orofacial clefts (58 patients) were prospectively enrolled into the study and screened for the presence of a 22q11 deletion. Detailed clinical evaluation, high-resolution chromosome and FISH analysis were performed.

Results

Deletions at 22q11.2 were detected in 9,4% (6/64) patients with CHD. In the subgroup of patients with conotruncal anomalies, 22q11.2 deletion was present in 17,8% (5/28) patients. None of the 58 patients with palatal abnormalities had a deletion.

Conclusions
Testing is recommended for patients with conotruncal heart defects, because a substantial proportion has a 22q11.2 deletion. Deletion testing of children with other cardiac defects should be considered in the presence of additional features of 22q11.2 DS. A routine screening for the 22q11.2 deletion in children with isolated palatal anomalies may not be justified.

Molecular Basis of Tooth Agenesis and Orofacial Clefts in the Polish Population
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Selective tooth agenesis and nonsyndromic cleft lip with or without cleft palate (CL/P) are the most common inherited craniofacial disorders in man. Despite this, little is known about the genetic defects responsible for these complex conditions. To date, many polymorphisms and several mutations correlated with these developmental malformations have been described. However, the results of the reported associations largely depend on the population and the geographical area of the world. The MSX1, PAX9, TGFα and IRF6, belong to the main candidate genes whose mutations are responsible for tooth agenesis as well as CL/P.

The aim of the report was the analysis of the main candidate genes responsible for tooth agenesis and orofacial clefts in a group of patients from the Polish population, in an attempt to explain the reason of these common developmental disorders.

The main results of the study of the candidate genes responsible for tooth agenesis were identification of three novel heterozygous mutations located in MSX1 and PAX9 that might cause severe oligodontia. One of them, a 151A>G transition, found in a highly conserved paired box sequence of PAX9 was the first de novo mutation described in this gene, suggesting that PAX9 might be a good candidate gene for an isolated form of tooth agenesis.
Analysis of candidate genes responsible for orofacial clefting revealed an association between two polymorphic variants of TGFα (BamHI, OR = 1,878; RsaI, OR = 1,627) and cleft lip, with or without cleft palate. As opposed to other populations, it was shown that polymorphic variants of MTHFR, IRF6, RARα and PAX9 were not associated with this common developmental disorder.

Our results provide the first step to identification of genes contributing to the aetiology of selective tooth agenesis, as well as cleft lip with or without cleft palate in the Polish population, and might provide an insight into better diagnosis and prevention of these common inherited disorders.

Molecular Pathogenesis of Hirschsprung Disease - The Significance of Polymorphisms of Ret Gene
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Hirschsprung disease (Hd) is a congenital disorder, characterized by the absence of intestinal ganglion cells. Various genes are included in the aetiology of Hirschsprung disease. Diverse models of inheritance, co-existence of numerous genetic disorders and detection of numerous chromosomal aberrations together with involvement of various genes confirm the genetic heterogeneity of Hd. Recent advances show that the aetiology of Hirschsprung disease focuses on the meaning of RET gene. There are plenty of different mutations in this gene. No mutation is fully penetrant and they have varying effects on the length of the aganglionic segment of the intestine. The aim of our study was to analyse single nucleotide polimorphisms (SNP) of RET gene in several exons. To test how the Hd phenotype may be affected by the presence of genetic variants, we compared the molecular results with clinical and long-term follow-up data. The study group comprised 120 patients. Molecular DNA analyses were performed in 60 cases. There were almost 4 times more affected

males than females. Family history for Hd was investigated only in four patients. We found a short segment of aganglionic gut in 64% and ultra-short segment in 16%, and long-segment in 20% of all patients. The 135A and 1296A and 2712G RET variant has been shown to be strongly associated with the Hd phenotype. Seven patients died in the endstage F508 was found, in other 5?of the illness, in two of them homozygous mutation patients genetic analysis was not performed. We have demonstrated that RET haplotypes containing these polimorphisms play a role in the aetiology of Hd. In the nearest future a genetic test and demonstration of mutation in genes involved aetiology of Hd could determine the severity of the clinical picture of Hd and the risk for Hd patient's family.

Chromosome 18 Trisomy - Edwards Syndrome in Patients of Department of Neonataology ICZMP (Polish Mother's Memorial Hospital Research Institution) in the Years 1993-2004

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Assumptions and Purpose

1. Defining the commonest phenotypic features of chromosome 18 trisomy.
2. Analysis of congenital abnormalities types observed in patients from an examined group.
3. Analysis of characteristic symptoms occurring during prenatal screening which may suggest the appearance of chromosome 18 trisomy.

Material and Methods

This study included 75 neonates born in ICZMP (Polish Mother's Memorial Hospital Research Institute) in the years 1993- 2004. Clinical diagnosis of chromosome 18 trisomy was verified every time by cytogenetic analysis based on cultivating peripheral blood lymphocytes. In some cases Edwards Syndrome was diagnosed prenatally. Material for the examination was obtained by amniocentesis or cordocentesis. Abnormalities were diagnosed on the basis of physical examination, echocardiogram, radiological and ultrasound imaging.

Results and Discussion

In analyzed group of 75 born- alive neonates with Edwards Syndrome (in the years 1993- 2004) there were 54,6% (41) of females and 45,3% of males (34). It was found that the commonest abnormal features that might suggest the chromosome 18 trisomy were: intrauterine growth retardation (retardation observed in 4th-9th week)- 95,8% (70 neonates), polihydramnion 89% (65 neonates) and congenital abnormalities concerning more than one organ 98,6% (75 neonates). Congenital heart defect was the commonest congenital abnormality in examined group 91% (67 neonates).

Conclusions

1. Coexistence of polihydramnion, intrauterine growth retardation and presence of congenital abnormalities may suggest the possibility of chromosome 18 trisomy occurrence in neonate.
2. The commonest complex of congenital abnormalities in chromosome 18 trisomy- Edwards syndrome, according to analyzed material, are congenital heart diseases (91%) (VSD, iAVC).
3. Other abnormalities occurring with congenital heart defects in Edwards Syndrome in examined group were: digestive tract abnormalities (31%), CNS abnormalities (27,7%).

Risk Factors of Babies with Congenital Birth Malformations

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Aim

Determination of priority risk factors of newborn babies with congenital malformations in Kyiv Region.

Volume and Methods
During 1999-2003 1206 newborns with congenital malformations were registered in Kyiv Region in the network of the Special State Genetic Monitoring Program. The group of healthy carried babies (975) was considered the control group. Risk factors influence was estimated by odds ratio calculation with 95% confidence interval.

Chronic infectious diseases were the priority factors of congenital malformations appearance risk. Chronic infectious diseases among women and men increased the probability of abnormal child birth (OR=2,96 with CI 1,98-4,44 for women and OR=6,62 with CI 2,48-19,20 for men).

Chronic extragenital diseases among women increased the probability of their giving birth to babies with congenital malformations (OR=1,79 with CI 1,43-2,25), including endocrine diseases (OR=1,27 with CI 1,00-1,60) and bad habits (smoking, drinking) (OR=2,00 with C? 1,47-2,71).

Occupational hazards among future parents also increased risk of their giving birth to babies with congenital malformations (OR=1,45 with C? 1,03-2,06 for women and OR=1,36 with C? 1,06-1,75 for men).

Conclusion
The determined risk factors are guided factors so there is a good possibility for primary prophylaxis of congenital and inherited pathology among newborns.

Birth Defect and Drug Exposure Surveillance in the Northern Netherlands
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Aim
Quantitative signal detection is a commonly used method to detect new adverse drug reactions (ADR) in spontaneous pharmacovigilance reporting systems. Since the occurrence of birth defects after maternal drug exposure can be seen as a specific type of ADR, we performed a survey on maternal drug use in the 1st trimester and the occurrence of birth defects in the offspring in our population based registry of congenital malformations.

Methods
We selected 3286 cases born between 1981 and 2003. Birth defects were coded according to ICD9 and ICD10. Drugs were coded according to the ATC-codes. We investigated combinations of 51 categories of malformations, not part of a chromosomal or monogenic disorder, with >= 10 subjects present and 60 groups of drugs with >= 10 exposed subjects present. As controls we used 669 subjects with a recognised chromosomal or monogenic disorder. For malformation-drug combinations with >= 2 exposed cases we measured the possible disproportionality by calculating the Chi2 and the proportional reporting ratio (PRR) with a 95% Confidence Interval (CI).

Results
In total 718 malformation-drug combinations had >= 2 exposed cases. For 87 combinations an increased risk was found with a p-value<0.05. Of these combinations 4 had a p-value < 0.01 and a lower PRR >=3: omphalocele x M01 (antirheumatic drugs), p=0.001, PRR=16.7, 95%CI=4.9-24.3; anorectal atresia x D01 (antifungals for dermatological use); p=0.004, PRR=12.4, 95%CI=3.3-15.3; malrotation of intestines x A06 (laxatives), p=0.004, PRR=10.7, 95%CI=3.3-14.4; microcephaly x J01EA (trimethoprim and derivates), p=0.005, PRR=44.6, 95%CI=4.2-50.7. Also ASD x N05BA01 (diazepam) had a p-value of 0.001, but the PRR could not be calculated because there were no

exposed controls. This method detected also the previously documented risk of exposure to fatty acid derivates (N03AG) and spina bifida (p=0.031, PRR=12.2, 95%CI=1.7-13.7).

Discussion

The combinations of drugs and malformations that are disproportionately present in our database may reveal signals of potential teratogenic drugs. However, the most strong signals are not described in literature before and the drug groups are heterogeneous. Therefore these results have to be interpreted carefully and critically. They have to be further evaluated, for example in an other database or by using analytic study designs.

Recreational Drug Use: A Major Risk Factor for Gastroschisis

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Aims

This study was designed to test the hypothesis that the risk of gastroschisis is positively associated with the use of recreational drugs in the weeks immediately following conception and to validate data collected at maternal interview concerning recreational drug use during pregnancy using maternal hair analysis.

Methods

A matched case control study was conducted in three UK health regions over the period January 2001 to August 2003. For each case, three live born controls were selected, matched by initial intended place of delivery, region and maternal age. Case note review and maternal interviews were used to collect information about risk factors for gastroschisis. Hair was collected for analysis to validate interview data concerning recreational drug use. Conditional logistic regression analysis was used to estimate the mutually adjusted odds ratios for gastroschisis associated with any recreational drug use and class A or B drug use. These estimates were revised using results from the hair analysis. Attributable risks were calculated.

Results

The adjusted odds ratio (aOR) for gastroschisis associated with first trimester use of any recreational drug during early pregnancy was 2.20 (95%CI 1.13 to 4.26) and class A or B drugs was 3.59 (95%CI 1.36 to 9.47). These statistically significant excess risks were increased to aOR 2.56 (95%CI 1.34 to 4.91) and aOR 3.82 (95%CI 1.58 to 9.22), respectively, when additional class A or B drug users, identified at hair analysis, were added to the analysis. The estimated attributable risk for gastroschisis of Class A or B drug use during early pregnancy was 6.7% (95%CI 1.7 to 23.4).

Conclusions

There is a significantly increased risk of gastroschisis associated with the use of recreational drugs in early pregnancy. The addition of class A or B drug users identified at hair analysis increased this risk further. However, although mothers who took Class A or B drugs in early pregnancy had an almost four fold risk of a gastroschisis pregnancy the estimated proportion of gastroschisis cases that were attributable to such drug use was less than 7%.

Maternal Obesity and Congenital Anomalies: Temporal Change in BMI in Emilia Romagna, Italy

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Aims

Obesity (defined as body mass index BMI > or = to 30kg/$m^{2)}$ is increasing across Europe. The International Obesity Task Force (IOTF) estimate that there are a billion adults overweight and over 300 million obese people world wide. Maternal obesity adversely impacts pregnancy outcome and has been associated with an increased risk for some types of congenital anomalies. Given the evidence from the literature regarding maternal prepregnancy obesity as a risk factor for some congenital anomalies and the increase in obesity reported for the general population a preliminary study was conducted using the IMER registry of congenital anomalies database to investigate if maternal prepregnancy obesity in mothers giving birth to babies with congenital anomalies is increasing over time and whether the prevalance by type of anomaly differs in obese and underweight mothers compared to the normal weight mothers.

Methods

The IMER registry of congenital anomalies covers the Emilia Romagna region of Italy: a population of 4 million inhabitants and around 25,000 births per year (http://www.unife.it/imer). IMER joined the EUROCAT network in 1980 (EUROCAT).As well as the variables collected for the EUROCAT database IMER runs a local database of other local variables. The maternal prepregnancy weight and height of mothers is routinely recorded on the IMER Congenital Anomalies notification form and entered in the IMER database. These parameters were used to calculate the body mass index (BMI) of non diabetic mothers giving birth to cases where BMI = kg/m2. BMI was classified as :

Under weight BMI <18
Normal BMI 18.5-24.9
Overweight BMI 25 to 29.5
Obese BMI > or = to 30kg/$m^{2.}$

Regression analysis was carried out on the maternal BMI per year over the 20 year period 1982-2002 to see if there is an increasing trend over time. This was compared to a limited database of control mothers (1982-1995). Mean height and weight by year was also plotted separetely. Further analysis of the data to establish if there are differences in OR by BMI (following Watkins et al.) was not conducted due to the lack of control data after 1995. The malformations recorded were divided into three groups: underweight mothers, normal weight mothers and overweight and obese mothers. The number of cases by type of malformation in each of these groups was calculated as a percentage and plotted graphically in order of the frequency in the normal weight mothers.

Results

The classification of mothers giving birth to babies with congenital anomalies by prepregnancy BMI category was conducted on the 9519 cases reported to IMER in the 20 year study period. 1787 cases were excluded as height or weight data was missing. Of the remaining 7732 cases the mothers were: Underweight (BMI <18.4) 628 cases (8.1%), Normal weight (BMI 18.5-24.9) 5729 cases (74.1%), Overweight (BMI 25 to 29.5) 1045 cases (13.5%) and Obese (BMI > or = to 30kg/m^{2}) 330 cases (4.3%). From regresion analysis of maternal prepregnancy BMI from 1982 to 2002 of cases and controls, the trend line shows maternal prepregnancy BMI to be increasing over time. When treated separately, both height and weight graphs showed an increase over time. In the study period mean height increased by 2.5cms while mean weight increased by 4.5 kgs. For certain types of malformation obese mothers represented a higher than expected percentage while underweight mothers a much lower than expected percentage (anencephaly , encephalocele, TOF). Gastroschisis and HLH on the other hand were higher than expected in underweight mothers and lower in obese women.

Conclusions

This preliminary study shows the trend for maternal prepregnancy BMI to be increasing over time in mothers giving birth to babies with congenital anomalies in Emilia Romagna whilst the control group seems to be remaining stable. However, caution is required in interpreting this data as limited data on controls was available. Even if we ignore the control trend it seems that in common with the general population in many countries, the sub group of maternal prepregnancy BMI in Emilia-Romagna is increasing with time. A change over time in both height and weight of mothers is seen. Underweight mothers seem to be more at risk for some congenital anomalies (eg. gastroschisis, HLH) and obese mothers less at risk than the normal weight mothers. The opposite is true for anencephaly encephalocele and TOF. Given that the literature has reported BMI as a risk factor for congenital anomalies attention should be payed by registries to gaining this data. Obesity like maternal age and smoking needs to be taken into account as a variable/ confounder in interpreting data on congenital anomalies . Maternal prepregnancy BMI is easy to calculate with the two variables height and weight normally recorded when a pregnant women checks in for antenatal care. A pregnancy in an overweight or obese women should be monitored with caution given the data in the literature regarding the lower detection rates by ultrasound of congenital malformations. Hence whilst maternal obesity represents a higher risk factor for congenital anomalies the probability of a prenatal diagnosis is lower. This needs to be taken into account in the interpretation of prevalence data as live births may be higher to obese mother due to lack of prenatal diagnosis and terminations. As shown from this preliminary study control information is needed in order to calculate odds ratios and counsel on increase risk of malformations for obese women. A large scale European study is recommended the results of which could lead to support in primary prevention.

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Prevention of Congenital Anomalies by Folic Acid Supplementation

L Abramsky

We have become very good at identifying pregnancies affected by a serious fetal abnormality, and in most European countries women may terminate an affected pregnancy if they wish. This is not primary prevention of the anomaly, and such terminations are great tragedies for the parents. It is important that wherever possible, measures are taken to reduce the number of conceptions resulting in fetuses with anomalies. Most efforts to prevent congenital anomalies have involved either removing teratogens from the environment of protecting pregnancy women from them. There are many examples of this strategy, but two good ones are vaccinating children against rubella and ensuring that pregnant women don't take Thalidomide. These strategies are very effective so long as they are well implemented. There are far fewer examples of preventing

anomalies by enhancing the intra-uterine environment. Indeed, whenever one is asked to produce an example, periconceptional folic acid is the standard answer. This talk will look at primary prevention concentrating on periconceptional folic acid supplementation and/or food fortification as a way of reducing the number of neural tube defects (NTDs) and possibly other anomalies. It will look at NTD rates in Europe during the first eleven years following publication of the MRA Vitamin Study in 1991 and at the question of fortification of a staple food.

The National Primary Prevention Program of Neural Tube Defects in Poland
E Mierzejewska, Z Brezezinski

The National Primary Prevention Program of Neural Tube Defects (NTD) has been developed in Poland since 1997 at the Department of Epidemiology of the National Institute of Mother and Child in Warsaw. It was financed by the Ministry of Health in 1998-2002, just after setting up the national recommendations for all women capable to be pregnant, to consume 0,4 mg of folic acid on a daily basis to reduce a risk of NTD in their babies.

The main aim of the Program is reduction of the prevalence of NTD in newborns through increasing folic acid intake among women in childbearing age. It was established that the incidence rate of NTD in newborns in Poland due to Program activities should lower by 35% to year 2005 and by 70% to year 2010. The Program is based on an informational and educational campaign directed to health professionals, women in childbearing age and secondary school students. Due to considerable differences among local communities the Program has been implemented through a network of provincial program coordinators from the Sanitary Epidemiological Stations responsible for the management of field program activities coordinated by the Central Program Office.

During the period of Program financing over 100 thousands educational books and booklets for medical doctors, nurses and midwives were edited, over 1 million educational materials (leaflets and posters) for women in childbearing age and secondary school students were distributed and over 2000 trainings for medical doctors, nurses and midwives were organized Over 1 million secondary school students participated in special educational program for youth “I can now help my baby to be healthy”. The Program has established its www pages with educational materials available.

Effectiveness of the Program has been assessed by changes in NTD mortality and morbidity rates, changes in women’s knowledge, attitude and behaviour concerning folic acid supplementation and changes in the amount of tablets containing 0,4 mg of folic acid sold.
During 1996-2002 years infant mortality caused by anencephaly decreased by 54% (from 24,8 to 11,3 per 100 000 live births) and infant mortality caused by spina bifida - by 59% (from 9,8 to 4,0 per 100 000 live births).

The repeated country–wide studies have shown, that although the percentage of non-pregnant women taking vitamin tablets containing folic acid did not increase (24,0% in 1999, 24,8% in 2003), 10,6% of women pregnant during the interviews in 1999 and 17,4% in 2003 began folic acid supplementation before pregnancy.

The first monovitamin tablet containing 0,4 mg of folic acid appeared in sale in 1999. Since then the sale trend of the tablet has been constantly increasing.

Prevention of NTDs with Folic Acid Supplementation and Food Fortification in British Columbia, Canada: Over a 10 Year Experience in a "Low Incidence Area"

M Van Allen, P Stathers, E Cairns, E Boyles, S Uh, P De Wals

Objectives

Folic acid (FA) supplementation has been shown to help prevent neural tube defects (NTDs). The protective effect is greater in high incidence areas compared to low incidence areas. Although, FA supplementation has been well studied, the effectiveness of food fortification with FA had not been studied prior to initiation of Public Health interventions. This study reports on the NTD incidence in British Columbia over a 10 year period, from 1992-200

Methods

This is a population based, retrospective chart review of prospectively ascertained cases evaluated in health centers in B.C. as well as cases reported to B.C. Health Status Registry. All NTD affected newborns, stillborns, therapeutically aborted fetuses and spontaneous losses $\geq$ 20 weeks born to mothers residing in B.C. were ascertained. The study time period was Jan. 1, 1992 through Dec. 31, 2002. Cases and anomalies were confirmed using medical records from multiple sources.

Results

Years	FA Initiatives	NTDs LB + SB + TABs	Total B.C. Births	Incidence
1992-1993	Pre-FA recommendations	113	92,511	1.22/1,000
1994-1996	FA supplements, Pre-Food fortification	146	140,431	1.05/1,000
1997-1998	FA supplements, Transition to fortified flour and cereal products	89	86,875	1.02/1,000
1999-2002	FA supplements, FO fortification	163	163,688	0.99/1,000

Discussion

Recommendations for FA tablet supplementation were initially issued by the U.S. CDC and PHS in 1992. Similar recommendations were issued in Canada in 1993, at which time it was estimated that 10% of the population were already taking multivitamins. In March 1996 the U.S. FDA approved FA fortification of enriched grain products, with fortification with 0.15 mg/100 gm grain starting Nov 1, 1998. Many U.S. firms started fortifying products shortly after March 1996. Health Canada approved a similar fortification plan, to be initiated by November 1, 1998. Because of Free Trade, U.S. products fortified with FA would have been available as early as March 1996. During the period of 1999-2000 all flour products as well as other food products would have been available to B.C. women. There was an unexpected increase in 1999 of 62 NTDs/42,040 births (1.47/1000) which otherwise obscures the overall decline in the NTD incidence. An overall decline of 37% in the NTD incidence of B.C. was observed as a result of FA initiatives. B.C. is a relatively low incidence area. Based on FA supplement intervention studies in China, we would anticipate that there were be a less dramatic reduction in B.C. compared to higher incidence areas of Canada. Newfoundland and

Labrador [Crane et al, 2001] reported a decline from 4.6/1000 in 1992-1996 to 1.2/1000 in 1998, a 74% reduction. Quebec reported a decline of 32% from 1.89/1000 in 1992-97 and 1.28/1000 in 1998-2000. [DeWals et al., 2003].

Conclusion

FA supplements and food fortification have been effective in reducing the NTD incidence in British Columbia and elsewhere in Canada. It is anticipated based, on the China study, that FA interventions are unlikely to reduce the population incidence below 0.6/1000.

EUROCAT Survey of Policies for Prenatal Screening for Fetal Anomaly Operating in European Countries

P Boyd, E Garner, C De Vigan

With recent advances in prenatal screening methods and with improved resolution and expertise at ultrasound scanning the questions of which screening test to use and when to offer ultrasound scans in pregnancy are difficult ones to answer. The availability of different resources, termination of pregnancy laws and social and cultural factors are important issues which vary in different countries. Different policies have been developed in different countries and in different areas within countries. This study aims to "map" the current state of prenatal diagnosis in countries in Europe which are members of EUROCAT. A questionnaire was developed to explore current (as in 2004) policies on prenatal screening for malformations (Down's syndrome and structural anomalies) and terminations of pregnancy for fetal anomaly. The questionnaire was sent to a previously nominated register leader from each country who was asked to contact all other registry leaders in their country about local policies. Responses have been received from 14 out of 18 leaders contacted.

Results

Screening for Down's Syndrome - National Policy: Nine (14 countries had some national policy) guidelines in place in 2004. The policies were different for each country - some used a maternal age cut off alone to offer a diagnostic test to older mothers, others used a mixture of maternal age screening and mid trimester (Triple) screening and/or nuchal translucency or mid trimester maternal serum screening to be offered to all women. One country had a screening policy based on a detection rate ie. a screening test should be offered that had a detection rate for Down's syndrome of >60% for a false positive rate of <5%. Of the five countries with no official national policy for prenatal screening, four offered a variety of maternal age screening, first and second trimester screening although for some women this is on a private basis.

Indications for prenatal cytogenetic diagnosis: In 11 out of 14 countries maternal age (usually ≥ 35 years) was given as an indication for prenatal cytogenetic diagnosis; in two this was only on offer (for Down's syndrome) after a screening test had been performed. One country did not offer prenatal cytogenetic diagnosis. Other indications for prenatal cytogenetic diagnosis were similar in all 13 countries ie. it was offered to translocation carriers, family history of chromosome anomaly and after ultrasound diagnosis of major malformations or certain soft markers.

Screening for structural anomalies by ultrasound scanning: 10 out of 14 countries had a national policy/recommendation regarding feta ultrasound scanning in place in 2004. These policies recommended an anomaly scan at 18-22 weeks with in most countries additional (morphometric) scans at 10-14 weeks and 29-32 weeks.

Termination of pregnancy for fetal anomaly (TOPFA): There is a very wide variation in the policies for TOPFA. In one country termination of pregnancy is illegal. The gestation limit for TOPFA varies from 12 weeks gestation to no limit. For most countries the limit is 22-24 weeks. In some countries later TOPFA is allowed if permission is sought from a special committee.

Cardiological Prenatal Diagnositc: A Fifteen-Year Experience
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Aim
The aim of the study was to present our own experience in prenatal diagnostics of congenital heart defects (CHD) and arrhythmias in fetuses of women with a higher risk of delivering child with a pathology of cardiovascular system.

Material and Methods
We retrospectively analysed 1,862 fetuses of women of the higher risk group. 1,980 prenatal echocardiographic examinations were performed. CHD was diagnosed in 152 fetuses and arrhythmia in 114.

Results
8% (152/1,862) of fetuses from teh studies group had CHDs. The most common conditions were Atrio-Ventricular Septal Defect (AVSD: 34 fetuses, 22.3%), Hypoplastic Left Heart Syndrome (HLHS: 19 fetuses, 12.5%), Ventricular Septal Defect (VSD: 16 fetuses, 10.5%) and Aortic Stenosis (AS: 10 fetuses, 6.6%). 18 (11.8%) patients with CHD died in utero and 9 (5.9%) shortly after birth. 65 (42.7%) underwent cardiosurgical correction after birth. In fetuses with arrhythmias (114/1,862, 6%) the most common conditions were extrasystoles (71 fetuses, 62.3%), supraventricular tachycardia (21 fetuses, 18.4%) and complete atrioventricular block (22 fetuses, 19.3%). 12 (10.5%) patients with arrhythmia died (9 in utero, 3 shortly after birth): 10 fetuses and 1 newborn died of complete atrioventricular block and congenital heart defect. All fetuses with supraventricular tachycardia were treated pharmacologically, 18 (85.7%) with good effect.

Conclusion
1. Fetal echocardiography enables early diagnosis of the CHD and fetal arrhythmias.
2. Prenatal diagnostics of teh CHD enables referral of the pregnant women to the Health Center, where cardiological and cardiosurgical treatment is possible.
3. The coexistence of the fetal complete atrioventricular block and CHD is associated with poor prognosis.

Ultrasound Diagnostic Schema for Determination of Increased Risk for Chromosomal Aneuploidies in Foetus in the First Half of Pregnancy
P Sieroszewski, E Bas-Budecka, M Perenc, J Suzin

Aim
The aim of the study was to work out early ultrasound diagnostic schema for the determination of increased risk for foetal chromosomal aneuploidies.

Material and methods
The study comprised population of 1318 pregnant women divided into 2 groups: 1255 women with normal course of pregnancy and 63 women with diagnosed fetal abnormalities. There were 34 cases of chromosomal abnormalities (trisomy 21, 18, 13, triploidy, unbalanced inversion 9, deletion 16) and 29 cases of structural malformations. Ultrasound scans were performed by Hitachi EUB 525 LI

digital scanner. The estimation of range normal values for the nuchal translucency (NT) measurement between 11 and 13 weeks and nasal bone length (NB) measurement between 12 and 20 weeks (correlation with biometric parameters – CRL and BPD) was performed.

The results obtained in the collective of normal pregnancies established a base for the calculation the range of normal values. The measurements of NB and NT showed linear value increase with the pregnancy course. For the nuchal translucency measurement correlated with CRL (38 – 85 mm) the values increased from 1,29 mm to 1,86 mm. Similar was the tendency for the nasal bone length which increased from 1,88 mm to 3,69 mm. Following test characteristics (correlation to CRL) were registered: NB – sensitivity 60%, specificity 98%, positive predictive value (PPV+) 43%, negative predictive value (NPV-) 98,9%. For the assumption that the test outcome means presence or absence of the nasal bone in the ultrasound scan sensitivity was 40% but specificity 100%; NT – sensitivity 63,6%, specificity 98,2%, PPV+ 38,9%, NPV- 98,2%; NT + NB – presents similar characteristic to the NB or NT alone - sensitivity 55,6%, specificity 98,6%, PPV+ 50%, NPV- 98,9%. The normal values of the markers in correlation with biparietal diameter BPD (20-55 mm) were observed as follows: nuchal translucency NT from 1,62 mm increases to 2,87 mm, nasal bone length NB from 2,52 mm to 7,29 mm. Following test characteristics for chromosomal aberrations markers (correlation to BPD) were noted: NB - sensitivity 68,4%, specificity 97,4%, PPV+ 56,5%, NPV- 98,4%; NT - sensitivity 73,9%, specificity 97,9%, PPV+ 54,8%, NPV- 99,2%; NT + NB - sensitivity 94,7%, specificity 98,9%, PPV+ 90%, NPV- 99,7%.

The “genetic sonogram” protocol for the structural defects detection was analysed: sensitivity was 80%, specificity 100%, PPV+ 100%, NPV- 99,7%.

Conclusions

1. The new biometric parameter – nasal bone length (NB) and corrected – nuchal translucency thickness (NT) are useful markers for fetal abnormalities, especially for chromosomal aberrations.
2. High predictive values of the diagnostic schema for the detection of aneuploidies and structural defects recommend its use in correlation with biparietal diameter (BPD).
3. The proposed schema is an effective algorithm for prenatal diagnostic characterised by high prognostic values.
4. The possible introduction of the schema could have an influence on the decrease of the invasive procedures rate, which could minimise the rate of miscarriages as complication of the amniocenteses.

Impact of Resource Centers of Parental Support Groups Creation and Development in Ukraine

W Wertelecki, T Vihovska, L Yevtushok

In Ukraine as well as in other post-soviet countries, there is no experience of effective activities of parental organisations. Besides, their number is very limited. Thus, planning the Ukrainian-American Birth Defects Program (UABDP) activities, we made maximum encouragement of education of parents with birth defects children and their joining together to be among our priorities. This task was assigned to 6 informational-resources centers (RC), created in the UABDP frames. The key elements of an RC are: trained information officers who are English-competent and knowledgeable of electronic information sources and web-technology; trained medical/clinical experts cognisant of BD, genetics and teratology; access to printed, electronic or web-based information resources; access to national and international consultants; RC staff located in major pediatric health care centers who, therefore, implicitly partake in RC activities; easy access to RC by professionals and the public through the extension of operating hours beyond standard working hours; electronic publication and dissemination of information resources developed by local

authors; partnerships with medical and other teaching/training programs. Today, RCs serve as a center for creation of new parental organisations and development of newly created. Using the existing resources parents get free access to contemporary information about new methods of treatment and rehabilitation of their children, establish contacts with similar parental organisations in Ukraine and abroad. Moreover, using foreign NGO's experience parents initiate and similar state administrative bodies to create modern facilities for social rehabilitation of children. That's why, we consider RCs to be the essential element stimulating parents of birth defects children for creation of parental support groups and their effective work.