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Primary Prevention of NTD by Periconceptional Folic Acid

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Prenatal Diagnosis of Congenital Heart Disease: Epidemiologic and Clinical Impact

Research Developmnents and Issues in the Prevention of Neural Tube Defects by Periconceptional Folic Acid

PN Kirke

It has been known since the early 1990's that folic acid taken periconceptionally prevents up to 70% of neural tube defects (NTDs). Although women's knowledge about the protective effect of folic acid has increased considerably during the past decade, studies in Europe and North American show that most pregnant women do not take folic acid periconceptionally. This reseach underlines the importance of implementing comprehensive and sustained health promotion campaigns to increase awarenes of the benefits of folic acid in preventing NTDs. The population subgroups in greatest need of this information are known: supplementation rates are low in young, poorly educated, unsupported and socially disadvantaged mothers. Unplanned pregnany is the strongest predictive factor for non-supplementation emphasising the urgency of considering food fortification as a complemtary public health intervention. Approximately half of the estimated 4,000 babies born with NTDs every year in the Eruopean Union could be prevented if public health programmes were in place to ensure that all pregnant wmen received sufficient folic acid around conception.

The ultimate measure of the effectiveness of periconceptional folic acid supplementation is a reduction in the population prevaence at birth of NTDs and it is somewhat surprising that the substantial increase in the reported use of periconceptional folic acid in England in recent years has not been accompanied by a clear cut reduction in the population prevalence. The reported increase of 29% in the use of folic acid supplementation before pregnancy in England from 1.8% in 1993 to 30.6% in 1997 (Wild J et al, 1997) would be expected to result in a fall in the NTD prevalence at birth rate of approximately 14% and some (but not all) recent reports are consistent with this estimate.

The main emphasis in current NTD research is on identifying genetic risk factors with particular emphasis on folate-related genes but now also branching out to examine other genes. It is hoped that the discovery of new genetic risk factors might reveal important gene-environment interactions which could result in better interventions for primary prevention.

A Comparison of Policies for the Prevention of Neural Tube Defects in Europe
J Goujard

Following research findings on the prevention of neural tube defects (NTD) by periconceptional folic acid in the years 1980-1992, from the first non-randomised studies in the UK to the MRC and Hungarian controlled trials, recommendations for a possible primary preventive strategy of these defects were developed in several European countries between 1992 (UK) and 2000 (France). These recommendations were first promulgated either by government agencies or by professional organisations in the fields of medicine or nutrition. Rare are now countries in Europe without a governmental ("official") policy regarding folic acid for NTD prevention.

In the 9 European countries we surveyed (England and Wales, Finland, France, Hungary, Ireland, Italy, Norway, The Netherlands, Portugal), the taget population is, for the most part, women planning a pregnancy, and the target period is from one month before expected conception through the first two months of pregnancy. Such recommendations, however, would not benefit the high proportion of unplanned pregnancies that occur in many European countries. In Portugal, the recommendation is that child-bearing women should be informed of the advantages of folic acid supplementation. In France, in 2000, the Ministry of Health and the French Committee of Health Education produced a booklet that encourages childbearing women to improve their nutrition, in particular their dietary folic intake.

Generally, the recommendation for prevention of recurrence is daily use of a supplement containing 4mg of folic acid during the periconceptional period. For the prevention of first occurrence, the current advice is the use of folid acid tablets with most commonly a daily dose of 0.4mg, and an increase of dietary folate intake.

The possibility of mandatory enrichment of cereal flours with folic acid, such as done in USA, is raised in England and Wales, In some countries, limited types of food fortified with folic acid, mainly breakfast cereals, are available. In Hungary, the initital production of fortified bread began in August 1998.

In some countries the issuance of recommendations was followed by public awareness campaigns and surveys to assess the effectiveness of and compliance with the recommendations. In some countries such as Ireland and the Netherlands, these efforts were directed at high risk subgroups of women (such as those of low socioeconomic class). Each point will be approached.

Periconceptional Folic Acid Supplmentation in Norway 1999-2000
LM Irgens

<u>Objectives</u>
In Norway, the recommendations issued to the public on periconceptional folic acid supplementation have been conflicting; while the National Board on Nutrition has reocmmended periconceptional use of 0.4mg folate in general and 4mg to prevent

recurence, the Inspectorate of Health has considered Norwegian nutrition in general to be adequate, through recommending specific items such as liver and vegetables. On the other hand, the message from professionals, through the media, has been unanimously pro supplementation. Thus, in Norway, the interest attached to the use of periconceptional folic acid supplementation in general, has a special background, and there is a particular need of an assessment.

Methods

In September 1999, the Norwegian SIDS Association launched an information campaign on risk factors for SIDS. An evaluation scheme was established to assess knowledge and practice with respect to these risk factors before and after the launch of the campaign. In addition a question on the use of vitamins was included. The questionnaire was mailed to all women in Norway having given birth in October and November 1995 and 1999 respectively, 13,657 women. Anonymous answers precluded a reminder. The response rate was 70.9%.

Results

In 1998, altogether 7.6% used folic acid supplementation at least 3 times a week against 20.5% in 1999. Supplementation was rare in young (<20 years) women, increasing from 4.7 to 8.1%. In women older than 35 years there was no effect of education level, but a strong effect of partiy; in birth order 1, 22.6% used folic acide against 8.8% in birth order 4+. Unmarried women used folic acide to the same extent as married women.

Conclusion

In Norway during the years 1998 and 1999, the periconceptional intake of folic acid increased but was still too low, particularly in young and multiparous women. Further information for the public is needed.

Trends in Knowledge and Use of Folic Acid in the Five Year Period 1996-2000

McDonnell R, Ward M, O'Leary M, Baschir N, Hoey J, Doyle A, Scallan E, Sayers G, Doyle D, Delany V and Johnson H

Background

Almost a decade has passed since recommendations were issued in Ireland and other countries on periconceptional use of folic acid 400µg by women of child-bearing age, to reduce the risk of giving birth to a child with a Neural Tube Defect (NTD). The principal means of achieving this goal have been the use of folic acid promotion campaigns, while in the meantime actively considering folic acid fortification of staple food stuffs.

Objective

To examine trends in women's knowledge and use of folic acid in the eastern region of Ireland over a five year period, as a measurement of the effectiveness of folic acid promotional campaigns.

Methods

300 antenatal women attending their initial booking appointment in three Dublin maternity hospitals were surveyed each year from 1996-2000. An interviewer administered questionnaire was used with questions on folic acid knowledge and intake, with demographic and obstetric questions. Differences in the demographic and obstetric characteristics of respondents during the 5 year period were examined using Chi-square tests. Trends in knowledge and intake of folic acid were anlysed using the Chi-square test for linear trend.

Results

The demographic and obstetric profiles of respondents were broadly similar in each year. The proportion who had heard of folic acid rose from 54% to 92% from 1996 to 2000 (x^2 test for trend: $p<0.001$). Knowedge that folic acid can prevent NTD also rose from 21% to 67% (x^2test for trend: $p<0.001$). Although the proportion who took folic acid during pregnncy increased from 14% to 74% from 1996 to 2000 (x^2 test for trend: $p<0.001$), periconceptional use stablised at approximately 20% after rising from a base of 6% in 1996. A similar pattern was observed in the proportions who reported being advised to take periconceptional folic acid.

Conclusion

The changing trends suggest that promotional campaigns have been markedly successful in broadening awareness of folic acid, but much less effective in promoting periconceptional use. This may due to the intermittent nature of folic acid promotion campaigns, the time lag between knowledge and behavioural change or other factors eg. unplanned pregnancy. Promotional campaigns need to be vigorous and continuous to be effective. The introduction of fortification of foodstuffs in Ireland should be strongly considered.

Prevalence of Neural Tube Defects in Bulgaria

Simeonov E, Avdjieva D and Dimitrov B

Previous studies have shown significant variations in the prevalence rate of NTD in different parts of Bulgaria: 1.5% in Sofia, Burgas and Gabrovo (1991), 3.9% in Pleven (1993), 11.02% in a small isolated community (Rudozem area - to the south of the country; 1996). The Rudozem cluster was found in a relatively isolated population of small size (13,000) and predominantly Muslim religion by means of retrospective (1983-1986) and prospective (1987-1992) studies over a ten years period (20 NTD fetuses/children registered in 1,804 pregnancies).

Registration of congenital anomalies (RCA) according to EUROCAT criteria provided more precise information concerning the prevalence rate of NTD int eh Sofia population over the period 1996-1999. 28,814 pregnancies have been followed and 60 NTD fetuses/newborn babies have been registered (2.08%) as follows: anencephaly-16; iniencephany-6; encephalocele-1; spina bifida-37.

Nineteen NTDs (32%) have been detected prenatally and pregnancies terminated; 14 were stillborn. A mild nonsignificant increase of incidence rate has been noted. All affected families were provided genetic information and recommendations for proper control of further pregnancies. Folate metabolism studies in 31 families and in a control group are now in progress.

Insufficient Folic Acid Intake in the Netherlands. What About the Future?
de Walle HEK and de Jong-van den Berg LTW

Background
In 1993 all women of childbearing age in the Netherlands were advised to take a daily 0.5mg folic acid pill in order to reduce the risk for neural tube defects. This study desribes both recent and past awareness and use of folic acid supplements in relation to socioeconomic status in the Northern Netherlands. The consequences of a recent report of the Dutch Health Council report will be discussed as well.
Methods
In the most recent cross-sectional study (November 2000), pregnant women filled out a questionnaire. Out of 473 women, 461 were willing to co-operate. The highest fulfilled level of education was taken as an indicator for socioeconomic status.

Results
77% (n=357) of the respondents had heard about folic acid before being pregnant. 63% (n=289) knew about the protective effect for NTDs and 33% (n=151) knew the entire advised period. 61% (n=265) of the respondents used folic acid in some part of the advised period and 36% (n=164) used it in the entire advised period. Higher educated women knew more about folic acid and used it significantly more often in the periconceptional period than lower educated women.

Conclusions
Since compliance to proper use of folic acid was poor, food forticification in the Netherlands must be seriously considered. The Dutch Health Council wants to limit the fortification of food products to those products that are especially aimed at women who wish to become pregnant. The fortification of specific products instead of staple foods is a missed chance to reduce NTDs and possibly other birth defects and cardiovascular defects as well.

Developments in the Treatment of Oral Clefts and Other Craniofacial Anomalies in Europe
Mossey P, Semb G and Shaw B

Developments in the surgical treatement of oral clefts
Some history and background regarding the organisation of surgical services in Europe, the recognition of the shortcomings and attempts to improve surgical protocols, surgical techniques and services. Research in scar free wound healing which would have a particular impact on cleft lip and palate repair is also ongoing.

Developments in the non-surgical management of oral clefts

Advances in non-surgical management of orofacial clefts will include prenatal diagnosis, pre-surgical orthopaedics, orthodontic therapy, speech therapy and psychology

- there is a need to examine the support services that underpin the prenatal diagnosis of cleft lip and palate.
- a randomised clinical trial of presurgical othopaedics was carried out in The Netherlands and the results reported.
- in Psychology, recent research reveals that parent-infant interactions during the first year of the child's life hold important consequences, not only for the child's later psychological development, but potentially also for CL(P) treatment protocols.
- orthodontic and speech therapy are part of the core services underpinning the management of OFC.

Strategies for improving clinical services for clefts and other CFA

A recent WHO/NIH initiative examined priorities for international collaborative research in clinical management and health service delivery issues:

- identification of optimal clinical interventions for the management of craniofacial anomalies (evidence based care)
- identification and dissemination of stragies to optimise quality of care delivered (quality improvement)
- identification of strategies to increase the availability of care to all effected citizens of the world (access and availability)

Strategies for improving treatment, understanding and prevention of CFA

A new four year programme of research, supported by the European Commissions Framework V programme, has been initiated. The project will harness a network of research arising from the integration of BIOMED II Project "Standards of Care for Cleft Lip and Palate in Europe: Eurocleft" and the European Science Foundation Special Interest Group on "Gene Environment Interaction in early Human Development: Demonstration Project on Orofacial Clefting". The clinical work includes:

- a multi-centre randomised trial of the primary surgery for infants with complete unilateral cleft lip and palate, testing four variations of surgical techniques
- dissemination of consensus statements and guildeines via publication, network, newsletters, targeted ifnroamtion to helath authorities
- assembly of a set of longitudinal clinical records of consecutive cases representative of "good practice" as a reference norm.
- critical appraisal of distraction osteogenesis will be undertaken as an exemplar for the appraisal of other complex, infrequent interventions. Recommendations concerning future European use and researche of this technology will be produced.

Gene Environment Interaction in Orofacial Clefts
Little J

Orofacial clefts are among the most common types of congenital anomaly, and affected children require multidisplinary surgical and nonsurgical care from birth until adulthood. Apart from the cost in terms of human suffering, the costs of care and social rehabilitation are high. Therefore, there is a need to identify possible strategies for primary prevention. There is accumulating evidence that maternal nutrition, smoking and alcohol consumption in early pregnancy are associated with risk of cleft lip and, to a lesser extent, cleft palate, but studies are inconsistent. There is evidence that these exposures also are associated with cleft palate, in some with a tendency for the associations to be weaker then for cleft lip. Exlcuding orofacial clefts is greater than can be accounted for by the tendency of family memebers to have similar exposures. In the presence of gene-environmental interaction, failure to take both sets of factors into account may result in bias in the estimate of relative risk. It is possible that the inconsistent associations with these exposures may in part be accounted for by different frequences of genetic polymorphisms that affect susceptibility. Examples of candidate polymorphisms include those identified from studies of gene expression in palatal development and/or as coding for growth factors, and those that may mediate the metabolism of exposures that may affect palatogenesis. The possible role of interaction between these polymorphisms and maternal nutrient intake, smoking and alcohol consumption in early pregnancy will be discussed.

Epidemiology of Oral Clefts in Europe
Bianchi F, Calzolari E and EUROCAT Working Group

In the framework of the EUROCAT Project (funded by the EU under the Rare Diseases Programme), data on Oral Clefts (OC) collected over a long period of time, were analysed. The 1980-96 EUROCAT database includes 9,553 cases with Cleft Palate (CP) or Cleft Lip/Palate (CLP) collected by 31 registries among 6,242,763 live and stillbirths. The prevalence at birth of any Oral Cleft (OC) was 15/10,000; 6.2/10,000 for CP and 9.0/10,000 for CLP. The well-known sex ratio difference betwwen CP and CL or CLP was confirmed Among these cases, 65.7% occurred as isolated anomalies, with a majority of CLP (73.5%). OC in chromosomal aberrations were observed in 1,542 cases (7.1%), while an OC occurred among recognised conditions in 1,732 cases (18.1%) and in 1,610 cases (16.1%) among multiple congenital anomalies of unknown origin. The proportion of induced abortions following prenatal diagnosis is small (6.8% for CP; 9.3% for CLP) and generally refers to more severe anomalies associated with OCs. The Pierre Robin sequence cases were 499 (0.8/10,000), the holoprosencephaly sequence cases 70 (0.1/10,000). Geographical distriubtion of OC in Europe is heterogeneous and points out different patterns for CP and CLP. Prevalence of OC is significantly higher in northern countries compared to southern countries. CLP exceeded CP in all Centres excepting in Malta, Scotland and Finland, which present a peculiar situation both for isolated CP and recognised conditions. The prevalence of the isolated conditions confirms, in general, the observations concerning the total cases, especially in the northern registries both for CP and CLP cases. A pattern of high prevalence of CP cases with MCA resulted in Northern Netherlands and three UK registries (Glasgow, Liverpool, Belfast). In a few centres

recognised conditions were observed in excess, both in CP and CLP cases. diagnositic ability, particularly in detecting syndromes, must be taken into account. The relevant heterogeneity observed among centres highlights the necessity of analysing data on the different oral cleft types taking into account the knowledge of genetics currently available as well as susceptibility and environment conditions in the different Europen areas, particularly with reference to the gene variants and nutritional habits.

Investigating the High Rate of Cleft Palate in Finland
Ritvanen A and Raitio J

Oral clefts are the most common congenital malformations worldwide. In Finland the total prevalence of clefts (live births, stillbirths and selective terminations) is very high compared with other Europen populations, 25.5/10,000 in 1993-1999. The cleft situation is also unusual with high prevalence of cleft palate (CP) 14.7/10,000 (3.6 for cleft lip, CL and 7.2 for cleft lip with cleft palate, CLP) and with increasing trend for all clefts and esecially for CP.

The Finnish Register of Congenital Malformations was established in 1963. It is national, population-based and run by the government. Its data collection was renovated in 1993 and it has now an active multisource case ascertainment. Data from all notified liveborn cleft cases is confirmed and complemented by the two cleft operating centres in Finland, by all stillbirths from death certificates and autopsy reports, and by pregnancy termination information from hospitals and from the national Abortion Register. In the Malformationm register there has been an ongoing epidemiological project on clefts in 1986-2000 in co-operation with the major cleft operating centre, HUSUKE.

The prevalence of clefts increased by a third in 1948-1974, for both Cp and CLP. The increasing trend has continued since 1975, but more for CP. The increase may be due to better reporting and to better case ascertainment by the Malformation register since the early 1990's, but also to decreasing perinatal and infant mortality and changing environment. In 1993-1999 there has, however, been a slight decrease of the prevalence of all cleft types, but more clearly of CP, which is probably due to later diagnosis and reporting of soft and especially submucous CP cases. The same trend is seen for both associated and isolated clefts. The annual variation of CP is bigger than of total CP.

The relative proportion of cleft types has been rather stable in 1993-1999 (57.7% for CP, 14.2 for CL, 28.1% for CLP). The prevalence of all and associated clefts has a slightly decreasing trend the more northwards and eastwards you go but there is no clear geographical trend fo rthe prevalence of isolated clefts. The ratio CP/total CLP is very unusual. In 1993-1999 it was 1.4 and a slightly increasing trend is seen over the years. It is also increasing towards theeast and north (both isolated and associated clefts). The same geographical trend is een for the prevalence of hard CP. In teh Oulu region up north the prevalence of CP is unusually high. The prevlance of total CLP decreases towards the east and north. This north/south and east/west difference is also seen with cardiovascular and some other general diseases and is probably due to both genetic and environmental differences and to the settlement history of our country. The ration CLP/CL is 2.0, which is also unusual.

Selective pregnancy terminations have been added to the Malformation Register since 21993. The relative proportion of terminations in teh cleft data in 1993-1999 is not high, 5.9% for all clefts and only 3.6% for CP, but 9.1% for CL with CP. The corresponding figures for assicated cleft cases are 16.7%, 9.5% and for CLP 27.9% which is mainly due to chromosomal cases. The terminations do not have much effect on the increasing trends over the years or with geographic variation.

The sex-ratio for all clefts is 0.9 (0.6 for P, 1.6 for CL, 1.6 for CLP). The relative proportion of CP by sex is 38.2%:61.5% and 60.9%:38.7% for total CLP.

The prevalence of all live births with cleft is 23.3/10,000 and of stillbirths 194.6 which is 8.4 fold greater in stillbirths than in livebirths. For cleft palate this ratio is amller: 5.8 (live births 13.9, stillbirths 80.1) and for total CLP 12.2 (live births 9.4, stillbirths 114.5). For associated clefts the corresponding figures are 21.1, 12.3 and 40.4.

The proportion of clefts associated with other malformations (minor anomalies excluded) is 34.6% (36.6% for CP, 19.4% for CL, 38.0% for CLP and 31.7% for total CLP. For hard palate the figure is 45%). Cleft palate is associated most often with Pierre-Robin sequence, but among the wide range of syndromes there are also some Finnish inherited diseases with clefts like Meckel and Hydroletalus syndromes and Diastrophic dysplasia. Van der Woude syndrome cases have been actively diagnosed and reported due to a Finnish research project.

Evaluation of the Use of Ultrasound Soft Markers for Prenatal Screening
Boyd P

With improvement in technology and technique over the last decade, ultrasound scanning has enabled better definition of the fetus. An increasing number of ultrasound "soft markers" have been recognised. These markers (such as nuchal thickening, choroid plexus cysts, echogenic bowel, mild ventriculomegaly, renal pelvic dilatation, echogenic cardias foci) are not structural abnormalities but rather ultrasound appearances (often transient) associated with increased risk of a mjaor abnormality such as a choromosome disorder. Most fetuses with an isolated ultrasound soft marker will be normal at birth.

There is no general agreement about the definition of individual soft markers or on their clinical signficance and management. Most studies reporting soft markers have been on selected populations. As a result following the "discovery" of a new marker there may be an overestimate of the risk for abnormality that is only recognised when studies defining low risk , unselected populations are published.

The Oxford Congenital Anomaly Register has registered ultrasound soft markers since 1991. The evolution of reporting the more common markers in an unselected poulation and their contribution to the detection of fetal anomalies have been studied from 1991 to 1999 inclusive in an unselected poopulation (51,781 deliveries). Reporting of ultrasound soft markers led to a one percent increase in the prenatal detection of congenital malformations

in the first half of the study period and 5% in the second. Alongside this increase in detection there was a nine folod increase in the number of women with whom a discussion concerning a marker took place, and who subsequently delivered an apparently normal baby.

Our understanding of the biology and natural history of soft markers is limited. Discussion with parents about the significance of a soft marker detected in their fetus causes confusion and anxiety. Large studies on low risk populations are needed to address the complex issues of detection rates, clinical significance, psychological sequelae, resource implications and comparison with other screening programmes for chromsome anomalies.

Operational Protocols After Diagnosis by Soft Markers
Monni G, Zoppi MA, Ibba RM, Floris M

Down's syndrome is the most frequent chromosomal abnormality at birth and advanced maternal age has been the first factor considered to offer invasive diagnosis of fetal karyotype. Abnormal levels of maternal serum biochemical markers in the second trimester are associated with trisomy 21, and their analysis has been introduced in clinical practice in most nations. Because a high percentage of trisomy 21 fetuses have structural abnormalities or manifest some nonpathologic sonographic soft markers (femur and humerus shortening, echogenic bowel, echogenic intracardiac foci, nuchal fold thickening, renal pylectasis, first trimester nuchal trasnlucency), these ultrasonographic findings have been used to adjust the maternal background risk for trisomy 21.

First trimester nuchal transluncey is the marker most useful in distinguishing fetuses with trisomy 21. It is used alone or in combination with first rimester biochemistry (PAPP-A and free beta hCG). In our four year's experience, based on the analysis of 10,262 pregnancies with 10,486 fetuses, nuchal trasnlucency was enlarged in 503 cases (4.8%), of which chromosomal abonormalities were present in 109 (64 trisomies 21); the sensitivity for chromosomal abnormalities was 74.3% (81/109), and the sensitivity for trisomy 21 was 76.5% (49/64).

Chorionic villus sampling (CVS) represents the earliest method of invasive prenatal diagnosis for chromosompathies. Transabdominal CVS (TA-CVS), performed at 10-12 weeks gestation is usually carried out by introducing a spinal needle into the chorion under ultrasound guidance, with a risk of fetal loss of 1-2%. Early amniocentesis is performed at 10-14 weeks gestations carries higher loss rates then TA-CVS, and a greater number of cases of talipes and respiratory problems, Standard amniocentesis is performed at 15 to 17 weeks, with a risk of 1% fetal loss, and is the technique of choice used for second trimester fetal karyotyping. The widespread diffusion of the earlier techniques has limited the indication of second trimester Fetal Blood Sampling for karyotyping, and this technique is now mostly reserved for cases of mosaicism or analysis failure.

Prenatal Screening for Down Syndrome in Europe
Cocchi G

Prenatal diagnosis of fetal aneuploidy is a continuously and rapidly evolving area of investigation. Down's syndrome (DS) prenatal screening, based on a variety of combinations of different techniques (multiple maternal serum markets and ultrasound investigation both in the first and in the second trimester, prenatal cytopgenetic diagnositic testing at any gestational age of the fetus), is a well established part of antenatal care. Currently in European countries the debate over the best screening policies (for example application of the techniques in the first trimester vs the second an choice of the maternal serum markers) related to the severla strategies adopted in the various countries, is still unresolved. The screening approach is able to identify about 50% fo the pregnancies with fetuses affected by trisomy 21, with some differences in the percentage of terminations of pregnancies (ToPs) in the Euroepan countries probably due to the different policies.

Within the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS), a specific survey and analysis of prenatal diagnosis of DS has been performed with the aim of assessing the progressive increase in the use and diffusion of prenatal diagnosis techniques and the impact of elective termination on prevalence rate at birth of DS in countries where elective abortions have been performed since 1993. In the years 1993-1998 in the European registries that provided a data set for 6 years, a regular increase in the proportion of aborted foetuses was observed: 41.5% in 1993, 45.9% in 1994, 48.5% in 1995, 50.9% in 1996, 52.2% in 1997 and 53.8% in 1998. This increase in ToP is due both to the group of older women (>-35 years) and younger women (<-34 years) event though most ToPs (about 63% in 1993 vs 65.3% in 1998) in comparison with the group of younger mothers (<-34 years) where the increase of ToP was more evident (24.7% in 1993 and 43.6% in 1998).

Thsi significant trend (P=0.0001) in the younger group (+76.5% in six years) may be explained by better identification of women who may be at risk from factors other than maternal age, as in England and Wales and in France, to a better knowledge of ultrasonographic signs in the first trimester (ie. fetal nuchal translucency screening, NT) and consequently a better yield of routine ultrasound, or it may be related to multiple-marker screening in other countries, as in Italy, which may explain the increased detection in the younger group of women. The combination of first trimester biochemical maternal serum markers and NT measurements may improve the efficacy of prenatal screening of DS.

Evaluation of Prenatal Diagnosis of Congenital Heart Diseases
Stoll C, Alembik Y, Dott B

<u>Objectives</u>
The objectives of this study were to evaluate prenatal diagnosis of congenital heart diseases (CHD) by fetal ultrasound (US) examination in a well-defined population.

Methods
This study was undertaken to evaluate routine prenatal detection of CHD by ultrasound scan in 93,208 consecutive pregnancies of known outcome from 1993 to 1999. Three US examinations, one for search of congenital anomalies and 2 for biometic purposes, were performed. CHD were classified as isolated or associated when at least one other major extra cardiac malformation was present. the associated CHD were subdivided into chromosomal, syndromic and multiple.

Results
Only 339 of 811 malformed fetuses with CHD without chromosomal anomalies were detected (41.8%). The sensitivity of detection varied from 61% for malformations such as hypoplastic left heart and single venticle, to around 5% for venticular and atrial septal defects. The prenatal detection rate of CHD was 16% for isolated cases, 41% for chromosomal anomalies, 55% for recognised nonchromosomal syndromes and 48% for multiple malformations. The gestational age at discovery varied from 16 to 35 weeks. There is no upper limit for termination of pregnancies in our country: 24% of the pregnancnies were terminated after prenatal diagnosis.

Conclusion
Our study shows large variation in the prenatal detection rate of CHD. Prenatal diagnosis of CHD is significantly higher if associated malformations are present. Cardiac defects affecting the size of the ventricles have the highest detection rate. Gestational age at discovery was 20-24 weeks for the majority of associated cardiac decects. Our results stress the need to obtain a definte, clear, four-chamber view and a view of the inflow and outflow tracks of the fetal heart, to perform scans after 18 weeks' gestation and to train sonogra[hers in order to improve prenatal detection of CHD.

Sex Chromsome Anomalies: How Likely are they to be Postnatally Diagnosed and how is the Prenatal Diagnosis First Communicated to Parents?
Abramsky L, Hall S, Levitan J, Marteau T, Chapple J

This paper will combine the results from two studies.

In the first study, our objectives were to estimate what proprtions of boys born with an undetected extra sex chromosome are diagnosed postnatally and what the indications for karyotyping are. Using our malformation register and records from all cytogenetic laboratories in our region, we ascertained all cases diagnosed pre and postanatally over a four year period. Comparing these figures with expected numbers from birth prevalence studies, we estimated that:

<10% of cases were prenatally diagnosed
26% of nonprenatally diagnosed 47,XXY men were postnatally diagnosed
12% of nonprenatally diagnosed 47,XYY men were postnatally diagnosed

In the second study, we investigated how the prenatal diagnosis of sex chromosome aneuploidy is first communicated to parents. Staff from cytogenetic laboratories notified us

when a suitable case was diagnosed. We then conducted a taped telephone interview with the staff who disclosed the result to the parents. We asked them what they had said and how they had said it. We also asked them what they knew and felt about the condition in question. One month and six months later, the parents were sent questionnaires about their general well being and their feelings about how they were give the diagnosis and what information they were given. We ascertained the pregnancy outcome from hospital records.

We identified great variation in what different healthcare professionals know, think and say about the same sex chromosome anomaly. The parents' response revealed that some were profoundly dissatisfied with the initial information they were given.

We conclude that some parents are given misleading information when they are first informed their fetus has a sex chromosome anomaly and that it is essential that all staff who communicate results to parents have accurate, up-to-date information about the condition identified.

Prenatal Ultrasound Detection of Abdominal Wall Defects: Associated Malformations, Chromosomal Abnormalities and Perinatal Outcome

Barisic I, Clementi M, Haeusler M, Gjergja Matejic R, Stoll C and EUROSCAN Study Group

Objectives

Evaluation of the current effectiveness of routine prenatal ultrasound screening in detecting abdominal wall defects and associated conditions in unselected poulations across Europe. Analysis of the impact of associated malformations, syndromes and chromosomal abnormalities on pregnancy outcome and parental decisions concerning termination of pregnancy (TOP).

Methods

19 Congenital Malformation Registires from 11 European countries collected data on the family history, mother, fetus/infant, results of prenatal scans and outcome of pregnancy. The study period was 30 months (01/07/96 to 31/12/98) and the total number of monitored pregnancies 690,123.

Results

From the total of 243 abdominal all defects, associated malformations were found in 56.2% (77/137) of omphalocele and 22.6% (24/106) of gastroschisis. Overall 25% (34/137) of fetuses with omphalocele had an abnormal karyotype, 31.4% (43/137) had a recongisable syndrome, association, or an unspecified pattern of malformations. Of the 106 gastroschisis 15 (14%) had additional anomalies. Only 2 (2%) cases could be attributed to a chromosomal and 7 (7%) to a recognisable nonchromosomal syndrome. Prenatal ultrasound examination detected 75% (103.137) of omphalocele and 83% (88/106) of gastroschisis. The detection rate was higher and the mean gestational age at detection lower in multiple affected fetuses. In 51 (37%) cases with ompahalocele and in 31 (29%) with gastrochisis, parents opted for TOP. Proportion of TOP was higher in multiple affected fetuses compared to isolated cases. The overall survival rate was 41% (56) for omphalocele and 73% (62) for

gastrochisis. The number of live-births was higher in isolated cases comapred to syndrome, chromosomal and multiple cases.

Conclusions
A high proportion of abdominal wall defects is associated with concurrent malformations and/or chromsomal abnormnalities. Associated conditions clearly influence perinatal outcome. Therefore, a detailed search for other structural malformations and karyotyping should be performed whenever an abdominal wall defect is identified.

Important of Ultrasonography in teh Prenatal Screening for Trisomy 21 in teh PArisian Population 1998-1999
de Vigan C, Vadovar V, Verite V, Goujard J, Goffinet F

Objective
To assess the importance of ultrasonography in the prenatal screening for trisomy 21 in the Parisian population.

Methods
Data were collected by the Paris Registry of Congenital Anomalies for all cases of trisomy 21 (births and terminations of pregnancy) in 1998-99. These data included information on the prenatal screening techniques used in each case. In France, 3 scans are usually performed during pregnancy, around 12, 22 and 32 weeks. The screening policy also includes maternal serum, offered to all mothers since 1997. Amniocentesis is sytematically proposed to mothers 38 years and older.

Results
267 cases of trisomy 21 were recorded during the two years (prevalence 36 per 10,000 births). In all 86% of the cases were prenatally diagnosed. From the 230 diagnosed cases, 55% were detected by ultrasonography: 38% with the first trimester scan through nuchal translucency measurement and 17% with the second trimester scan showing cardiac malformations and also small signs. The contriubtion of other techniques was less: 26% of the detected cases came from amniocentesis for maternal age, 17% from maternal serum screening and 2% from the third trimester scan. Anomalies observed during the first and second trimester scans will be detailed.

This high prenatal detection by ultrasound was observed despite the fact that only 82% of mothers had access to the first trimester scan. Moreover, the estimated sensitivity of nuchal translucency measurement in this population study was rather low: 49% when considering the results with the response "normal" or "abnormal" (n=180), incresaing to 57% when considering only the 96 cases with the nuchal measurement in millimetres.

Conclusions
This study shows that nuchal translucency measurement expended quickly and became the first tool in the Parisian population for the prenatal screening of trisomy 21, long before maternal serum screening.

One Year Follow Up Study of Antenatally Diagnosed Dilated Renal Pelves Between 5 and 9.99 mm within Merseyside and Cheshire, UK

Edwards G, Harrison J

Merseyside and Cheshire is a survey that covers around 28,000 births.

Objectives

To identify those fetuses and babies in whom the ultrasound finding of renal pelvis dilatation was reported to the Mersey Congenital Anomaly survey in 1996.

To follow up a selected population of babies with an initial diagnosis of mild, dilated renal pelves (5-9.9mm).

Methods

Data was obtained on all babies reported to the Mersey Congenital Anomaly Survey with unilateral or bilateral dilatation of the renal pelvis. By retrospective casenote analysis and/or obtaining copies of radiological reports.

Results

There were 250 cases of dilated renal pelves reported to the Mersey Congenital Anomaly Survey. 195 of these babies had an initial diagnosis of renal pelvis dilatation of between 5 and 9.9 mm. 191 of these babies (76.5%) were diagnosed on rountine anomaly scan. 75% of this sample had bilateral dilatation, 25% had unilateral dilatation, 11% had other associated ultrasound findings. 12 (6.2% underwent karyotyping. 44% had resolved by the third trimester. 30% had resolved by the first postnatal scan and 7.5% had resolved by subsequent postnatal scan of less than 1 year. However, 13.5% of cases were still affected by 1 year of age and 5% of cases were not followed up until resolution of dilated renal pelves.

Conclusion

In 18 cases, dilatation persisted until at least 1 year of age. Therefore, if measurements of less than 10mm were considered normal, 6 babies with significant dilatation at 1 year of age would not have been followed up.

In Memory of Zachery Johnson: Congenital Anomalies in Ireland

Johnson H, McDonnell R, Delany V

Background

The Dublin EUROCAT Registry was set up in 1979 by the Medico-Social Research Board as one of the first registries leading to the formation of EUROCAT. In 1989, the Health Information Unit was established in the Eastern Regional Health Authority (formerly the Eastern Health Board), with Dr Zachery Johnson as its Director. The Registry was transferred to this unit and the many thousands of manual records were computerised. The Registry covers the eastern region, accounting for one-third (~20,000/annum) of the births nationally. Zachery was appointed to the central Steering Committee of EUROCAT, and in 1997 the registry became an associate member of the International Clearninghouse for Birth Defects Monitoring Systems.

Work of the Registry

The Registry has studied the epidemiology of Down Syndrome in collaboration with the Galway Registry, together with a 10-year survival study of children with the syndrome. Given Ireland's history of a high NTD prevlance, the Dublin Registry devoted considerable attention to the condition. In 1995, a study found poor knowledge and minimal compliance with the international recommendations on the perconceptional use of folic acid. A Folic Acid Action Group was established and repeat surveys are being done annually. Between 1997-1998, three new registries were set up in cooperation with the Dublin Registry, covering almost two thirds of the country, with the eventual aim of national coverage. Due to concerns in other areas, reticence in supplying data to registries has threatened the supply of essential data, but it is hoped that these issues will be satisfactorily resolved. Recent increases in diaphragmatic anomalies and gastroschisis are being investigated by case-control studies, and a study of anomalies in proximity to landfill sites has just been completed.

The 20-Year Report

A report covering 17 years of surveillance by the registry was almost complete when Zachery became ill in 1999. A 20-year report (1980-1999) dedicated to his memory will be published shortly and we believe he would be very rpoud to see his great work being continued.

Epidemiology of Congenital Anomalies in Sicily

Bianca S

Objectives

To describe the epidemiology of congenital anomalies (CA) in Sicily using data from teh Sicilarn Registry of Congenital Malformations (ISMAC Registry).

Materials and Methods

The Registry started in 1991 on a voluntary basis to monitor congenital malformations in Sicily. Reports are obtained from delivery untis, pediatic units, and other specialist departments. From 1991 to 1998 a total of 260,867 newborns were surveyed with 5,584 malformed cases (2.14%). The territorial covered percentage is different in the nine provinces of Sicily. We are also members of EUROCAT and ICBDMS.

Results

In the years we monitoring congenital anomalies in Sicily, no variations in incidence were evident, with no variation in the time trend. Some areas with high risk for CA were montiored to search for a cluster. This year, a cluster of CA was suspected in a high industrial area, but our first result needs more studies to evaluate the possible correlation between the high prevalence of bierth defects and pollution. To evaluate the impact of prenatal diagnosis on birth prevalence, a study was started in January 2000 to collect terminations of pregnancy for CA.

Conclusion
The Registry is important for monitoring CA incidence, More studies are needed to improve the monitoring possibilities of our Registry and the sue of the collected data.

Risk of Chromosomal Congenital Anomalies in Relation to Residence Near Hazardous Waster Landfill Sites in Europe
Vrijheid M, Dolk H, Armstrong B and the EUROHAZCON Collaborative Group

Background
The EUROHAZCON study previously reported a 33% increase in risk of nonchromosomal anomalies for residents living within 3km of hazardous waste landfill sites in 7 European countries. This paper reports finsing from the EUROHAZCON study on congenital anomalies of chromosomal origin.

Methods
Data were collected from eight regional congenital malformation registers in five European countries. The study included a total of 245 cases of chromosomal anomaly (live births, stillbirths and terminations of pregnancy) and 2412 nonmalformed controls, selected around 23 landfill sites. A zone of 3km around the landfill sites was defined as the zone of most likely exposure. In analyses this 3km proximate zone was compared with a 3-7km "distant" zone.

Results
Results show an increase in risk of chromosomal anomalies for people living lcose to hazardouse waste landfill sties (0-3km) compared to further away (3-7km). The odds ration was 1.41 (95% CI 1.00-1.00) after adjustment for potential confounding factors, maternal age and socioeconomic status. There was little evidence of a consistent decline in risk with distance from landfill sites. Odds ratios were raised but did not reach statistical significance for Down syndrome (OR 1.36, 95% CI 0.86-2.14) and non-Down syndrome anomalies (OR 1.64, 95% CI 0.92-2.95).

Conclusions
Our data suggest an increase in risk of chromosomal anomalies similar to that found for nonchromosomal anomalies, and cannot be readily explained by confounding factors or bias. More study into the chemical causation of chromosomal anomalies as well as into residential expsoure to landfill sites is needed to interpret these findings.

Parental Occupation in Agriculture and Risk of Hypospadias: A Multicentre Case-Control Study in Italy
Bianchi F, Pierini A, Catalano S, Linzalone N, Rial M, Clementi M, Tenconi R, Calzolari E, Scarano G, Bianca S

Background
Parental occupation in agriculture has been frequently asociated with selected birth defects. Hypospadias has been proposed as one of the possible adverse reproductive

outcomes of exposure to endocrine disrupting chemicals. Among these disruptors some are commonly used in agriculature activities (eg. organochlorine pesticides, dioxins, phytoestrogens, PCBs). Recurrent inconsistent results and small sample size justify a multicentre case-control study to investigate rare esposures and diseases.

Objectives
To investigate the association between parental work in agriculture and risk of hypospadias in offspring.

Methods
The Italian regional registries network of birth defect (Nord Est Italia, Emilia Romagna, Toscana, Campania, Sicilia Sud Occidentale) provides population-based data. Malformed newborns and induced abortions are routinely registered by each registry within the area covered using standardised procedures in accordance with the EUROCAT-European Surveillance Programme guidelines. Cases are infants with hypospadias born during 1992-1998. Controls are healthy newborns (N E Italia and Emilia Romagna registires) or newborns with minor congenital malformations (Toscana, Campania, Sicilia S-O registries), matched for date of birth and residence area. Maternal and paternal agriculture work during pregnancy and some confounding variales among cases and controls were obtained by the routine collection.

Results
Among a total of 1,154,182 consecutive surveyed births, 868 cases (C), 4,874 healthy controls (HC) and 1,130 malformed controls (MC) were considered. Parents involved in agrocultural activities were 72 among cases, 277 among healthy controls and 77 among malformed controls. Maternal agriculture work did not increase the risk compared either to healthy or sick controls, whereas a significnt increase emerged for paternal work (OR C-HC 1.44; 95% CI 1.07-1.94, OR C-MC 1.53; 95% CI 1.04-2.25). The risk estimation for phypospaidas pooling HC and MC was OR 1.46, 95% 10.09-1.95.

Conclusion
High variability of considered hypospadias, missing information on individual expsoure to endocrine disruptors and the lack of confounding factors in the risk estimation have reperesented, at this stage, the limitations of the study; therefore results are mostly descriptive. The main objective of this ingoing study will be to tackle these problems to confirm or not the identifed association between parental occupation in agriculture and risk of hypospadias in offspring, specifying type and extent of exposure.

Congenital Anomalies: Experience of a Regional Registry for Heart Defects 1980-1994 (Italy)

Clazolari E, Garani G, Cocchi G, Magnani C, Astolfi G, Volpato S, Bosi G, Rivieri F, Miolo GM

Objectives
To understand etiologic and genetic factors and to evaluate prevention programs via creation of an interdiscriplinary regional registry of congenital anomalies. To study trends over an extended period of time - the 15 years from 1980 until 1994.

Materials and Methods

During the study period 1,549 stillborn and livebortn babies affected by Congenital Heart Defects (CHD) out of 330,017 consecutive births (4.7 per 1,000) were studied. Malformations were coded and congenital heart defects defined for each case. The risk of familial recurrence of cardiac lesions was estimated and interesting families for further molecular genetic analysis identified. Data from induced abortions were not available during this period.

Results

During the study period 1,549 (12 stillborn: 0.8%) patients with a CHD were ascertained among 330,017 births (4.7 per 1,000). A temporal trend in the prevalence of CHD shows a range between 3.1 and 6.4 per thousand births. Among the 1,537 live born babies, 186 died within 6 months. 1,164 cases have been classified as affected by simple CHD and 178 as affected by complex CHD. Among the simple CHD, isolated ventricular septal defect represents the most common lesion (1.8 per 1,000) followed by isolated atrial septal defect type ostium secundum, Pulmonary valvar stenosis and atrioventricular septal defect with a prevalence of 0.25 per 1,000. Tetralogy of Fallot, patent ductus arteriosus in mature babies, and transposition of the great arteries have a prevalence ranging from 0.08 to 0.24 per 1,000. Hyposplastic left heart syndrome and coarctation of aorta have a prevalence of about 0.1 per 1,000. The frequency of complex CHD was 11.5% (178 cases). Pulmonary atresia with or without VSD and double inlet ventricle account for about 27%, common arterial trunk 14%, tricuspid valve atresia 11% and Ebstein's anomaly 3%. Conotruncal defects had a total frequency of 12.1% (188/1549); TGA represents the most frequent CHD (0.24 per 1,000). Isolated VSD and ASD II had a slight female excess (male/female ratio 0.87 and 0.71 respectively). Among CTD, defects a male predominance in TGA and TF (male/female 2.23 and 10.4 respectively); and a female predominance in common arterial trunk (male/female 0.90) were found. The most frequently associated non-cardiac lesions were: genito-urinary (22.9%), musculoskeletal (25.3%) and gastrointestinal anomalies (11.5%). In 59 CHDs (59/179; 33%), two other systems were involved. A recognised condition was detected in 69 (4.5%). A standard karyotype was performed in 300 out of the 1,549 CHD (19.4%) and a chromosomal anomaly was detected in 152 (142/1,549; 9.8%). The recurrence risk (RR) calcuated for isolated CHD was 2.3% in sibs and 2.0% in parents affected by CHD.

Conclusions

A homogeneous group of patients has been identified for further etiologic and genetic studies. The creation of a standardised system for the nationwide recording of congenital heart defects designed with regard to the sources of ascertainment, diagnostic criteria, and the system of classification is emphasised.

Folic Acid Antagonists (Trimethoprim-Sulfonamides and Sulfonamides) During Pregnancy and the Risk of Orofacial Clefts

Czeizel AE

Antifolate agents can induce multiple congenital abnormalities, neural tube defects and cardiovascular and other malformations in animal experiments and in the humans. The

objective of the study was to check the human teratogenic potential of two trimethoprim-sulfonamide combinations with some antifolate effect: trimedthoprim-sulfamethoxazole cotrimoxazole) and trimethoprim-sulfomethazine, in addition sulfasalazine and other sulfonamide treatments during pregnancy. Pair analysis of cases with congenital abnormalities and matched population controls was performed in the large population-based dataset of the Hungarian Case-Control Surveillance of Congenital Abnormalities between 1980 and 1996. 38,151 pregnant women who had newborn infants without any congenital abnormalities (control group) and 22,865 case pregnancy women who had newborns or fetuses with congenital abonormalities were evaluated. In the case group, 351 (1.5%) and in the control group , 443 (1.2%) pregnancy women were treated with cotrimoxazole (crude OR; 1.3 with 95% CI: 1.1-1.5). In additional 45 (0.2%) case and 39 (0.1%) control pregnancy women had trimethoprim-sulfamethazine treatment (crude OR: 1.9 with 95% CI: 1.3-3.0). A higher rate of multiple congenital abnormalities (including mainly urinary tract and cardiovascular abnormalities) was found in case infants born to mothers with cotrimoxazole treatment during the second-third months of pregnancy. In addition a higher rate of cardiovascular abnormalities occurred in the case groups with cotrimoxazole, trimethoprim-sulfamethazine and sulfathourea treatment during pregnancy, respectively. Sulfasalazine did not indicate any teratogenic potential. Treatment with cotrimoxazole during pregnancy may increase the risk of cardiovascular abnormalities and particularly multiple congenital abnormalities including defects of urinary and cardiovascular system. A higher rate of cardiovascular abnormalities was also found after the treament of trimethoprim-sulfamethazine and sulfathiourea during pregnancy.

Comparison of Clinical Findings and Echocardiographic Examination of Newborns with Trisomy 21: Analysis of 32,589 Newborns of the Mainz Congenital Birth Defect Monitoring System

Wiesel A, Stolz G, Schlaefer K, Queisser-Luft A

Trisomy 21 is the most common chromosomal aberration. In about half of the infants with trisomy 21, the chromosomal defect is combined with heart defects as well as other major malformations. The exact correlation between cardiac murmur and the prevalence of heart defects in infants with trisomy 21 is not known. It was the aim of the study to investigate the correlation between cardiac murmur and the prevalence of heart defects in infants with trrisomy 21 based on the Mainz Congenital Birth Defect Monitoring System.

Over a period of 10 years (1990-1999) 32, 589 livebirths, stillbirths and abortions recorded in the Mainz birth registry underwent standardised physical and sonographic examination in the first week of life. In all children with clinically suspected trisomy 21 as well as for all stillbirths and abortions, chromosomal anlsyses were routinely performed. An echocardiogram was routinely obtained for all newborns with trisomy 21. The pathological findings in stillbirths and abortions were used for the identification and classification of heart defects.

Ninety-one infants with trisomy 21 were diagnosed: 49 (53.8%) livebirths, 6 (6.6%) stillbirths, 30 (33.0%) induced abortions and 6 (6.6%) spontaeous abortions. The total prevalence was 28 cases with trisomy 21 per 10,000 pregnancies. The average age of the

mothers was 30.5 years for newborns and 35.5 years for sillbirths and abortions. A heart defect was diagnosed by echocardiogram in 25 of the 49 liveborn babies; only 11 (44.0%) infants had auscultatory findings. The prevalence rate for heart defects was 40.6% (37/91), including the diagnosis of stillbirths and abortions. The two most common heart defects were atrio-ventricular defects (20; 54.1%) and ventircular septum defects (5; 13.5%).

The prevalence of infants with trisomy 21 is about 1 per 400 pregnancies, in our population-based registry. A heart defect was diagnosed in 40.6% of all children. These results are in accordance with the literature. Only 44.0% of the livebirths with heart defects had a cardiac murmur. We conclude that all infants with trisomy 21 should routinely undergo an echocardiogram during the first week of life. The detection of a heart defect is crucial for the quality of life and outcome in children with trisomy 21 and enables optimal therapy and family guidance.

Cluster of Birth Defects in an Industrial Area of Sicily

Bianca S, Madeddu A, Contino ML, Tisano F, Petrucci MP, Ettore G, Sciacca S

Objectives

A cluster of birth defects is defined as an aggregation in time and/or space of malformed cases. Clusters of adverse reproductive outcomes are reported with increasing frequency and the media or clincians are most often the initiators of the alarm. Often the existence of registries provided the relaiable estimation of the expected number and etiological evaluation.

Materials and Methods

In January-February 2001, the media reported a cluster of congenital anomalies, born during the year 2000, in Augusta, a highly industrial area of South East Sicily. We evaluated data on malformed newborns from the Sicilian Registry of Congenital Malformations (ISMAC Registry) database (388 malformed cases in a total of 16,288 newborns) and data on neonatal mortality for birth defects from the Territorial Pathology Registry (RTP Registry) of cases born in the 21 cities of Siracusa province from 1995 to 2000. Data on induced abortions were not available.

Results

The evaluation of birth defects showed a mean prevalence for all Siracusa province of 23.9/1,000 newborns. In Augusta, the mean prevalence was 31.4/1,000. A high prevalence was found in all the coastal areas where the chemical industries are located. When we evaluated the type of anomaly, we found that in this area hypospadia (including all types of hypospadia) was present in 6.5/1,000 three times higher than the province mean. We also found, in the same area, about 3/1,000 cases of venticular septal defect and of cryptorchidism. When we evaluated the mortality rate of malformed newborns we found hgih values still in the same geographic area.

Conclusion

We think that the presence of the two registries (ISMAC and RTP) was useful in providing a reliable estimation of prevalence and in providing a result to community; in fact, in cluster management the community's perception of a cluster may be more important than establishing the scientific existence of a cluster as suggested by Read and Borman in 1997. We also think that this first result needs more studies to evaluate the possible correlation between the high prevalence of birth defects and pollution.

Prenatal Diagnosis of Congenital Heart Disease: Epidemiologic and Clinical Impact

Cocchi G, Mazzoni E, Canzi A, Gualdi S, Capelli M, Prandstraller D, Picchio FM, Perolo A, Mammoliti PMA

Congenital heart disease (CHD) occurs in about 8% of live births, and represents one of the main causes of perinatal death in developed countries. Today fetal echocardiography has become a routine prenatal diagnosis (PND) technique; moreover it has allowed a reduction of neonatal mortality and a better prognosis *quoad vitam*. Within the network of IMER Register, the Centre of Bologna Hospital has activated since January 1998 a follow-up survey, in cooperation with the Paediatric Cardiology Unit of Bologna, that analyses the clinical course of every newborn with prenatal or postnatal diagnosis of CHD. The study includes every newborn with CHD diagnoais entered into the IMER Register from January 1998 until March 2000. Newborns have been divided into two different groups according to the time of diagnosis; before birth/in the first week of life. In both groups we evaluated the presence of associated malformations or syndromes and the impact of PND on short term and long term outcome. The number and time of surgical treatments have been studied and related to the presence of a prenatal ecocardiogrpahic diagnosis.

In the entire surveyed period we observed 101 cases of CHD, 5 (4.9%) of them were prenatally interrupted and 96 were born alive. The prevalence at birth was about 11.4%. Seventy-five affected had an isolated CHD and 52% of them had a PND; 26 had associated defects and 73% of them had a PND. The most frequent CHDs were ventricular septal defects (VSD) and atrial septal defect (ASD), both with low percentage of PND, but with a very good prognosis. The groups of intermediate incidence include: transposition of the great vessels (TGV, 9 cases with 100% PND); pulmonary valve anomalies (PVA, 9 cases with 89% PND); hypoplastic left heart (HLH, 8 cases with 100% PND); tetralogy of Fallot (TOF, 8 cases with 75% PND). Thirty-nine of 53 newborns with PND underwent surgical treatment, 26 of them in the first days of life. The other 14 benefitted from an admission in a third level center for diagnostic investigation and, if necessary, intensive care, followed by an elective surgical treatment. This group had a high mortality rate (28.2%) probably because of the associated malformations and the severity of their condition.

PND of CHD does not alter short-term outcome but it optimises the management of the children with a CHD especially in the cases of ductus-dependency, avoiding low systematic flow, with multiorgan damage and/or cerebral hypoxia. In the long term these results could allow an improvement of the cardiac and neurologist development of the child.