

## **7th EUROCAT European Symposium Heidelberg, Germany, 30 May 2003**

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### **Follow up of Children with Fetal Echogenic Bowel with Particular Reference to Bowel Symptoms** *PA Boyd, Y Patel, P Chamberlain and K Lakhoo*

#### Objective

To determine whether there was any evidence of long-term bowel pathology in children, apparently healthy at birth, who had a prenatal second trimester diagnosis of isolated Grade 2 fetal echogenic bowel.

#### Method

This was a retrospective study on a defined, unselected population, using data from the Oxford Congenital Anomaly Register. Fetuses with isolated grade 2 fetal echogenic bowel and date of delivery 1994-2000 inclusive were identified. Information about the health of the children, particularly relating to bowel symptoms, was obtained from hospital records and from a questionnaire sent to the General Practitioner.

#### Results

109 cases were identified with delivery details available for 108. There was one unexplained intrauterine death and additional problems were subsequently diagnosed in four cases (cystic fibrosis(2), Down's Syndrome (1), VACTERL (1)). Questionnaires were sent to the GPs of the 103 who had no problems identified at the time of discharge from the Maternity hospital. Age at follow up ranged from 1 to 4 years. Responses to the questionnaires were received from 83 (81%). Of these 74 (90%) had not reported bowel symptoms to the GP, 9 (11%) reported symptoms relating to constipation (6), chronic abdominal pain (1), infantile colic with milk intolerance (1) and gastro-oesophageal reflux (1). Results from a control group will also be report.

### Conclusions

This small study provides some reassurance that there was no evidence for any serious long-term bowel pathology associated with isolated fetal echogenic bowel.

### **The Maternal Age Specific Prevalence of Down Syndrome**

*JK Morris, DE Mutton, E Alberman*

#### Introduction

The National Down Syndrome Cytogenetic Register (NDSCR) has registered reports from all cytogenetic laboratories in England and Wales of all pre- and post-natal diagnoses of a Down's Syndrome (DS) karyotype since 1st January 1989. The register now includes over 17,000 cases, with their maternal age, gestation at diagnosis, reasons for referral, any screening methods used, the karyotype and the outcome of prenatally diagnosed cases. It is the largest series of data on the prevalence of Down Syndrome.

#### Methods

We used this data to revise the estimates of maternal age specific live birth prevalence of Down Syndrome in the absence of antenatal screening and selective termination. We compared our estimates with all other published estimates.

#### Results

The age specific rates for Down Syndrome births were remarkably similar in all published series of data for women up until the age of 35, reasonably similar for women aged 35-45, but differed for women older than 45. Data from the NDSCR suggest that the prevalence of Down Syndrome does not continue increasing at an increasing rate with age above age 45 as has been previously assumed.

#### Conclusion

In practice the overall small differences in age-related risk between the different studies will not materially affect the performance of antenatal screening for Down Syndrome. More data is needed to clarify the pattern of risk with maternal age among women over 45 years old.

### **The Effect of IVF Treatment on Births and on the Perinatal Health of Children in Finland, 1998-2001**

*A Ritvanen, M Gissler, S Sihvo*

#### Introduction

In the 1998-2001 period, on average 2,710 IVF cycles and 1,870 ICSI cycles were started annually in Finland, and approximately 2,490 frozen embryos were transferred. This corresponds to about 5.7 treatments per 1,000 women of fertile age.

#### Methods

We studied the effect of fertilisation treatments (referred to as IVF from here on) on the most important birth and perinatal indicators. The National Medical Birth Register and the Malformation Register at STAKES were used as sources for data on pregnancies resulting from IVF treatment (N = 4,702 deliveries and 5,699 births); other pregnancies were used as controls (N = 219,086 deliveries and 227,463 births).

## Results

2.1% of all deliveries were the result of IVF. The proportion was substantially higher in twin (26%) and triplet (59%) deliveries. There were remarkably few IVF births in March and September, which probably is due to summer and Christmas holidays at the IVF clinics. However, this had no effect on the distribution of all deliveries by month. The average age of IVF-parturients was 33.5 years, compared to 29.8 years for the other parturients. IVF mothers were more often 35 years or more than were all other parturients (37% versus 18%) and primiparas (68% versus 41%). IVF mothers gave birth more often by Caesarean section (33% versus 16%) or by vacuum extraction or forceps (10% versus 6%). The proportion of IVF deliveries among all Caesarean sections was 4.2% and among all vacuum extractor/forceps deliveries it was 3.5%. 2.5% of all births were IVF children. More than every third IVF child (35%) was from a multiple birth, and because of that IVF children had more perinatal problems. compared to other children, they were more often born before the 37th gestational week (29.0% versus 4.2%). IVF children made up in total 11.0% of all prematurely born children and 11.8% of all low birth-weight children. In spite of the risk factors, the perinatal mortality of IVF children was only slightly higher than that of other newborn children (1.0% versus 0.6%). IVF births made up 4.3% of all perinatal deaths. IVF children more often had significant congenital malformations than did other children (all births: prevalence 397 versus 293/10,000; singletons: 418 versus 290/10,000 births).

## **The Risk of Major Birth Defects Associated with ICSI and IVF**

*JJ Kurinczuk, M Hansen, C Bower, S Webb*

### Background

The health outcomes for the offspring, including major birth defects, are an important aspect of the evaluation of assisted conception procedures. There has been limited research in this area and much of the available information has suffered from small sample sizes and inappropriate comparison data.

### Methods

The records of infants, born 1993-1997, from Western Australian registers (Reproductive Technology Register, Midwives' Notification of Birth System, Birth Defects Registry) were linked to examine the prevalence of major birth defects diagnosed by 1 year of age in infants conceived following intracytoplasmic sperm injection (n = 301), standard in-vitro fertilisation (n = 837) and natural conception (n = 4,000).

### Results

26 (8.6%) of the ICSI infants, 75 (9.0%) of the IVF infants and 168 (4.2) of the naturally conceived infants were diagnosed with a major birth defect by 1 year of age. Infants born following ICSI and IVF were more than twice as likely to be diagnosed with a major birth defect compared to naturally conceived infants; with odds ratios of 2.0 (95% CI 1.3-3.2) and 2.0 (95% CI 1.5-2.9), respectively having adjusted for maternal age, parity, infant sex and correlation between siblings. The results remained essentially unchanged following restriction of the analysis to term singletons. The list of birth defects was examined by an independent Paediatrician blind to conception status, in order to identify defects that may have been diagnosed due to increased diagnostic surveillance and which may not otherwise have been detected in a child age less than 1 year. When the infants with these defects were removed the inferences remained unchanged. ICSI and IVF conceived infants were more likely to have multiple major defects and to have chromosomal and musculoskeletal defects.

### Conclusions

in this study we used comparable data for the three groups of infants. The two-fold excess risk of major birth defects associated with assisted conception procedures did not appear to be due to increased diagnostic vigilance for the assisted conception infants. These results have important implications for the counselling of couples embarking upon assisted conception treatment.

### **ICSI: An Increased Risk for Major Malformations**

*A Wiesel, G Stolz, K Bauer, K Schlaefer, M Schmidt, A Queisser-Luft*

#### Introduction

The wish for a genetically own child is unfulfilled in about 10-15% of couples in Germany. Since its introduction in 1993 ICSI is the treatment of choice for cases due to severe male infertility. An increased risk of congenital malformations in children born after ICSI is discussed controversially until now. The aim of this study was to determine the prevalence of major malformations after ICSI conception in a population based birth cohort.

#### Probands and Methods

During the study period (1994-2001) 20,161 livebirths, stillbirths, spontaneous and induced abortions were examined according to a standardised procedure. A population based case-control study was performed to determine specific associations between major malformations and anamnestic risk factors. Cases were all newborns with (N = 1,331), and controls all newborns (N = 18,830) without major malformations. Assisted reproductive techniques and hormone therapy were tested as risk factors. The results for the ICSI and IVF cohort were compared. Relative risks were described as Odds Ratio with 95% confidence interval.

#### Results

Major malformations were diagnosed in 6.6% of all newborns. 950 (4.7%) pregnancies occurred after treatment of infertility, 85 (0.4%) of them after ICSI, and 202 (1.0%) after IVF. The calculated odds ratio for hormone therapy [OR 0.9 (0.7-1.30)] and in vitro fertilisation [OR 1.3(0.8-2.2)] did not reach statistical significance. However, newborns after ICSI had significantly increased risks for major malformations, univariate [OR 3.1 (1.7-5.4)] and multivariate [OR 2.7 (1.5-4.8)]. Logistic regression models were calculated for ICSI versus IVF and showed a significant elevated odds ratio [OR 2.4 (1.1-5.2)]. MM were diagnosed in 15 children born after ICSI conception. The distribution of the malformations to organ categories did not show a significant change.

### Conclusions

An increased prevalence of MM in newborns was identified after ICSI. Although ICSI and IVF couples share approximately the same genetic and anamnestic background, an elevated risk remains on the ICSI side. Couples undergoing ICSI therapy should be informed of the higher risk of major malformations (including chromosome aberrations), and should receive adequate genetic counselling.

### **Knowledge About Folic Acid Among Pregnancy Women in Finland**

*A Ritvanen, M Gissler, S Sihvo*

#### Introduction

Recent studies have shown that the risk for neural tube defects, NTDs (anencephaly and spina bifida), can be reduced by using folic acid supplements periconceptionally. The Nordic recommendation for the daily allowance of folic acid/folates for pregnant women is 0.4 mg. At

present, Finnish women get approximately 0.24 mg of folates from their diet. Neither the use of folic acid supplements in ordinary pregnancies nor food enrichment with folic acid in order to prevent NTDs has been considered necessary in Finland.

#### Aim

The purpose of this study was to find out whether Finnish pregnant women know about folic acid and whether they have used vitamin supplements containing folic acid during early pregnancy.

#### Method

The study was carried out in year 2000 in 114 public maternity clinics around Finland. A public health nurse or a midwife conducted a questionnaire interview with the women during their first visit to the maternity clinic. 547 women participated in the study (6% refused).

#### Results

The women had their first antenatal visit on average during the ninth gestational week. 65% of the women had heard about folic acid, young and less educated women less other than others. The women had got information on the effect of folic acid on pregnancy and fetuses from newspapers and magazines, public maternity clinics and health care centres, and from schools and other educational institutions. Drug advertisements and friends were more important information sources than were doctors and pharmacists. 10% of women knew about the effects of folic acid on pregnancy and the fetus. 29% of women could list at least one food product containing folic acid. 45% of women had used at least one preparation containing vitamins and/or trace elements before and/or in early pregnancy.

#### Conclusion

Although the majority of the women had heard about folic acid, their knowledge on its effects and on good nutritional sources of folates was poor. Information on the importance of periconceptional use of folic acids should be targeted in particular at young women in schools and other educational institutions.

### **Three Years After the Campaign Folic Acid Use Further Increased in the Northern Netherlands**

*HEK de Walle, LTW de Jong-van den Berg*

#### Background

In 1995, a mass media campaign about periconceptional use of folic acid in order to reduce the risk of fetal neural tube defects (NTD) took place in the Netherlands. In the fall of 1996, a small mass medial campaign was performed, but since then information to the public was left to private initiative.

#### Objective

We investigated periconceptional use of folic acid tablets 3 years after the campaign in the Northern Netherlands, a region where three previous awareness studies took place.

#### Methods

The present study took place in 1998. Pregnant women at their obstetrician or midwife were asked to fill out a questionnaire. From the previous studies only the cases from the Northern Netherlands were included.

### Results

A total of 453 women filled out the questionnaire in 1998. Of these women, 85% planned their pregnancy. Of all women 74% heard before pregnancy about folic acid, for women who planned their pregnancy this was 78%. The percentage of pregnant women who used folic acid during the entire recommended period increased from 0.4% in 1994 to 35.5% in 1998. For use during any part of advised period the percentage was 7.8 in 1994 and 62.5 in 1998.

### Conclusion

In absence of any formal campaign activities, the awareness increased 3 years after the 1995 campaign. The general goals of the mass media campaign were that 70% of women planning a pregnancy should know of the recommended advice and that 65% of women who knew of the advice before pregnancy should use it during the entire recommended period. The first goal was achieved in 1996 and the second goal has been approached in 1998 when 51% of these women used folic acid during the entire recommended period. The Dutch figures on awareness and periconceptional use of folic acid are higher than any figures reported in the literature so far.

## **Knowledge, Attitude and Practice of Croatian Women Regarding Periconceptional Folic Acid Intake -Preliminary Data**

*I Barisic, M Kos, R Gjergja, F Stipoljev, T Hafner, V Tokic*

### Background

The adequate periconceptional intake of folic acid (FA) prevents neural tube defects and FA supplementation or food fortification are now officially recommended in many countries. There are still no official FA supplementation guidelines or laws regulating food fortification policy in Croatia. So far there are as well no studies in our country of awareness of women in childbearing age regarding FA supplementation.

### Aim

To assess the knowledge, attitude and practice of pregnancy women regarding periconceptional FA intake in Croatia.

### Methods

A total of 180 pregnancy women completed the questionnaire during their attendance of prenatal clinic. General Hospital "Sveti Duh", Zagreb, in February 2003. The questionnaire was anonymous and on voluntary basis.

### Results

The medium age was 29.8 years ( $\pm 3.6$ ). 64% (115/180) of women were aware of FA role in preventing birth defects. They got information mostly from the media (50%), health professionals (37%) and friends (13%). Of those, 60% got the information too late, during (53%) or after the first pregnancy (7%). Most of them (86%; 155/180) was not satisfied with acquired knowledge and wanted to know more. Of women interviewed, 69% (125/180) were taking FA, but only 25% (31/125) during appropriate periconceptional period despite the fact that actual pregnancies were largely planned (60%; 108/180). Most of the women (72%) were not sure about the taken daily dosage. Women not taking FA (31% or 55/180) were less educated compared to the group of women taking FA (20% versus 45% of women graduated from faculty or high school) ( $P < 0.01$ ). Parity, marital and economic status did not influence FA intake. From 108 planned pregnancies, only in 29% (31/108) FA was administered during adequate time period, while 31% (33/108) did not take FA at all.

### Conclusion

There is a strong need for public health education initiative with official recommendations from Croatian Paediatric and Gynaecologic Societies concerning FA supplementation in our country. The education initiative should be conducted by the health care professionals and targeted to the awareness of the childbearing population about the need of the introduction of the new dietary habits for the prevention of birth defects.

### **Folic Acid Supplementation in Europe: Summary of the EUROCAT Report**

*L Abramsky, A Busby, based on work of the EUROCAT Folic Acid Working Group*

### Introduction

The aim of this report is to establish what action has been taken across Europe in relation to periconceptional folic acid supplementation and/or food fortification and what effect this is having on the prevalence of NTDs in Europe.

### Methods

Representatives from 17 countries participating in EUROCAT provided information about the folic acid situation in their country. NTD rates were extracted from the Central registry database for 1980-2000.

### Results

At the beginning of 2002, official governmental recommendation that women planning a pregnancy should take 0.4 mg of folic acid supplementation daily was in operation in 9 of the 17 countries. The earliest of those countries to introduce an official supplementation policy was the UK in 1992 and the latest was Spain in 2001. In the remaining eight participating countries, no official government recommendation about supplementation was in place, however, professional bodies within a subset had in fact recommended supplementation. While foods fortified with folic acid were available in many countries surveyed, none of them had introduced mandatory fortification. The seven countries that had official health education initiatives were Denmark, France, Ireland, the Netherlands, Norway, Poland and the UK. Studies in most countries suggested that the majority of women remained unaware of the protective effect of folic acid and only a tiny minority took it at the appropriate time. Women in Ireland, the UK, the Netherlands and Norway were found to be more likely to know about and take supplementation.

### Discussion

Periconceptional supplementation depends on pregnancies being planned. In most countries it is not known what percentage of pregnancies are "planned". Estimates went from 85% in the Netherlands to 10-20% in Poland. Representatives from eight countries had no information on the proportion of pregnancies that are planned. In the UK and Ireland there has been a marked decline in NTD rates over the years studied, particularly during the 1980s, and no significant association between NTD rates and the introduction of supplementation policy was found that could be distinguished from the pre-existing decline in rate. In the rest of Europe rates have been relatively stable over time, and there is some evidence for a reduction in NTD rates in countries and years in which there is an official supplementation policy (RR 0.67 95% CI 0.47-0.97).

### Conclusion

The potential for preventing neural tube defects by periconceptional folic acid supplementation is still far from being fulfilled in Europe.

## **A Pathogenetic System for Classification of Blastogenetic Defects**

*H Metzke*

### Introduction

The developmental field concept of Opitz (1982, 1986) is a hierarchical system with the horizontal levels primary field, progenitor fields and secondary (epimorphic) fields. Opitz defined the development fields as "basic biologic units of individual development and of evolution, and association to represent the idiopathic occurrence of multiple congenital anomalies during blastogenesis".

### Objective

The principle is generally accepted, but it was not possible so far to classify all cases with multiple malformations in this way. In continuation of the fundamental idea of Opitz, a vertical system of relatively independent but partly overlapping main developmental cascades (MDCs) will be demonstrated in this lecture:

- differentiation of great body cavities
- closure of neural tube
- development of notochord axis (some hedgehog cascade)
- development of extremities

It is possible to class many of the blastogenetic defects as combination of teratological series of this MDCs. It will be demonstrated on the VATER "association" and its demarcation from other blastogenetic symptom complexes - for example:

- limb body wall complex as combination of MDCs
- combination of amelia and malformations of the VATER complex
- axial mesodermal dysplasia spectrum
- oculoauriculovertebral spectrum as malformation complex of the notochord axis
- combination of urogenital malformations and anal atresia as end of the teratological series of OEIS

### Conclusion

In summary, a pathogenetic system for classification of blastogenetic defects is suggested, which make it possible to classify most of the clinical cases.

## **Congenital Malformations - Etiological Factors 20 Years After Kalter and Warkany**

*C Rosch, V Steinbicker*

### Objective

In order to determine whether a shift in etiological frequency spectrum has resulted 20 years later, data from the population-based malformation registry (1987-2000) all diagnoses of births with major malformations were analysed. The selection of etiological factors from the papers from Kalter and Warkany.

### Methods

The analysis is based on 143,335 births in the registration area. Major malformations were recorded in this investigation time period. The diagnoses from 4146 births concerning their etiology were analysed. The registration time period is limited to live births up to the completion of the first week of life.



## Results

Causes of Congenital Malformations (%)	Kalter and Warkany (1983)	Malformation-Monitoring Centre (2002)
Mendelian disorders - single gene	7.5	8.3
Chromosomal disorders	6.0	7.3
Environmental causes - Teratogens	5.0	2.0
Polygenic multifactorial Malformations*	20.0	48.8
Unknown cases	61.5	33.6

## Conclusion

Although the parts of monogenic and chromosomal disorders are comparable to the results of Kalter and Warkany, environmentally caused malformations appeared noticeably less often. The proportion of multifactorial malformations is more than double as high which is clearly the cause of the decline of unknown causes. Among other factors, the improved diagnosis by ultrasound screening of neonates is responsible for the high percentage of multifactorial caused malformations.

## Is Fetal Death of a Co-Twin a Significant Cause of Congenital Anomalies?

*POD Pharoah, D Anand*

### Background

Many congenital anomalies are consistent with having been caused by an ischaemic insult. We hypothesise that atresias and stenoses of the cardiac valves and the gut atresias have an ischaemic origin due to twin-twin transfusion. This may be associated with early loss of one twin.

### Aim

To compare prevalence of atresias and stenoses of the cardiac valves and the gut atresias in like and unlike twins.

### Methods

National England and Wales data were obtained from (i) all stillbirth and death certificates from twin registrations 1993 to 2000; (ii) for 1993-1995, where one twin had been a fetal or infant death, an enquiry was made of all general practitioners for congenital anomalies in the surviving co-twin; (iii) notifications of congenital anomalies in surviving twins born 1997-2000. The prevalence of congenital anomalies in like and unlike sex twins was compared.

### Results

	Deaths		Survivors		Total	
	Like Sex	Unlike Sex	Like Sex	Unlike Sex	Like Sex	Unlike Sex
Valve stenosis or atresia	31	10	6	1	37	11
Gut atresia	11	3	23	5	34	8

Among all twins in England and Wales 1993-2000, the ratio of like to unlike pairs is 2:1. The observed ratio of 4:1 for these congenital anomalies shows a significant excess ( $P < 0.02$ ).

### Conclusion

The data sources used do not allow the separation between mono- and di-zygotic twins. As all monozygotic twins are of like sex, these results support the hypothesis that zygosity is important in the pathogenesis of the congenital anomalies. Within monozygosity, monochorionicity with twin-to-twin transfusion circulatory imbalance must be considered as a pathogenetic mechanism. These congenital anomalies in apparent singletons may be associated with unrecognised loss of a monochorionic twin very early in gestation.

### **Results of Response of Families at Risk to the Information on Genetic Counselling - Data from the Polish Registry of Congenital Malformations**

*A Latos-Bielenska, A Materna-Kirylyuk, JP Mejnartowicz, R Glazar, M Wisniewska*

#### Aims

In Poland a very low proportion of families at genetic risk is referred to genetic counselling clinics after delivery of a child with congenital malformations. The aim of the study was to establish the proportion of families at risk interested in genetic counselling after having provided them with proper information on aims and possibilities of genetic counselling.

#### Methods

The study involved 5733 children registered by the PRCM, born between 1st January 2000 and 30th June 2002 from mothers resident in the area of seven selected provinces of Poland. Every notification to the registry had been reviewed by an experienced clinical geneticist-dysmorphologist.

The children and their families were classified according to the type of malformation and family history as having a high, medium or low need of genetic counselling.

#### Results

1324 children with chromosomal aberrations, known syndromes or multiple malformations, central nervous systems malformations, renal agenesis, polycystic kidney, skeletal dysplasias, severe malformation of skeletal system, as well as children with other malformations with positive family history or high-recurrence risk were included in the high need group. From that group 474 children were excluded from the studies due to lack of their parents' consent for being contacted by the genetic counselling clinic. The remaining families (837) were sent information on indications,

purposes and possibilities of genetic counselling together with addresses of respective regional genetic counselling services, 219 families (26.2%) asked for genetic counselling, with the highest response in the multiple malformation group (49.6%).

#### Conclusion

The Polish Registry of Congenital Malformations remains a valuable identification source of the families at risk and a significant means of genetic care support form such families in Poland.