

**Papers published by members of the International Clearinghouse for Birth Defects Surveillance and Research and appeared in the Medline in the period September 2007 - March 2008**

**AL GAZALI L**

Al-Gazali L, Hertecant J, Algawi K, El Teraifi H, Dattani M. **A new autosomal recessive syndrome of ocular colobomas, ichthyosis, brain malformations and endocrine abnormalities in an inbred Emirati family.** Am J Med Genet A. 2008 Feb 12 [Epub ahead of print]

Department of Paediatrics, Faculty of Medicine and Health Sciences, UAE University, Al Ain, United Arab Emirates.

We report on an inbred Emirati family of Baluchi origin with ocular colobomas, ichthyosis, and endocrine abnormalities associated with midline brain malformations and mental retardation. All affected children had ocular colobomas, developmental delay and midline brain malformations. Hypoplastic pituitary gland was present in all three investigated children. Ichthyosiform dermatitis appeared in infancy in all surviving children. Other variable features include congenital heart defects, hypertrichosis and dark skin involving the dorsum of hands and feet associated with mild degree of palmo-plantar keratoderma. Some of the features in this family overlap the CHIME (Coloboma of the eye, Heart defect, Ichthyosiform dermatosis, Mental retardation, and Ear defect) syndrome. However, several features described in CHIME syndrome were not present in these children.

These include deafness, seizures, oligodontia, and hair abnormalities. Some of the features in these children also overlap with septo-optic dysplasia (SOD) but optic nerve hypoplasia, mandatory for the diagnosis of SOD, was present in one child only. We suggest that these children have a new autosomal recessive syndrome of ocular colobomas and ichthyosis.

\* \* \*

Rauch A, Thiel CT, Schindler D, Wick U, Crow YJ, Ekici AB, van Essen AJ, Goecke TO, Al-Gazali L, Chrzanowska KH, Zweier C, Brunner HG, Becker K, Curry CJ, Dallapiccola B, Devriendt K, Dörfler A, Kinning E, Megarbane A, Meinecke P, Semple RK, Spranger S, Toutain A, Trembath RC, Voss E, Wilson L, Hennekam R, de Zegher F, Dörr HG, Reis A. **Mutations in the pericentrin (PCNT) gene cause primordial dwarfism.** Science. 2008 Feb 8;319(5864):816-9.

Comment in:

Science. 2008 Feb 8;319(5864):732-3.

Institute of Human Genetics, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany. Anita.Rauch@humgenet.uni-erlangen.de

Fundamental processes influencing human growth can be revealed by studying extreme short stature. Using genetic linkage analysis, we find that biallelic loss-of-function mutations in the centrosomal pericentrin (PCNT) gene on chromosome 21q22.3 cause microcephalic osteodysplastic primordial dwarfism type II (MOPD II) in 25 patients. Adults with this rare inherited condition have an average height of 100 centimeters and a brain size comparable to that of a 3-month-old baby, but are of near-normal intelligence. Absence of PCNT results in disorganized mitotic spindles and missegregation of chromosomes. Mutations in related genes are known to cause primary microcephaly (MCPH1, CDK5RAP2, ASPM, and CENPJ).

\* \* \*

Taban M, Memoracion-Peralta DS, Wang H, Al-Gazali L, Traboulsi EI. **Cohen syndrome: report of nine cases and review of the literature, with emphasis on ophthalmic features.** J AAPOS. 2007 Oct;11(5):431-7. Epub 2007 Mar 26.

Department of Pediatric Ophthalmology and the Center for Genetic Eye Diseases, Cole Eye Institute, The Cleveland Clinic Foundation, Cleveland, OH 44195, USA.

**PURPOSE:** To review the clinical features of reported cases of Cohen syndrome with a focus on ophthalmic features and report nine new cases.

**METHODS:** Retrospective case series and literature review.

**RESULTS:** Cohen syndrome is a rare autosomal-recessive condition with about 136 reported cases. The typical phenotype of Cohen syndrome is variable and includes mild to severe psychomotor retardation, microcephaly, a cheerful disposition, characteristic facial features, childhood hypotonia and joint laxity, truncal obesity, intermittent neutropenia, along with a progressive retinal dystrophy and refractive myopia. We present nine cases that illustrate the typical clinical features of the disorder at different ages, including a woman with the less common finding of ectopia lentis.

**CONCLUSIONS:** Cohen syndrome remains underdiagnosed or misdiagnosed by ophthalmologists. Awareness of this condition among ophthalmologists is important because the typical systemic and ophthalmologic findings may lead to an accurate diagnosis and counseling. Although diagnostic criteria exist based on clinical studies of patients with confirmed VPS13B (COH1) gene mutations, no minimal clinical diagnostic criteria are widely accepted at this time.

## **ANNEREN G**

Annerén G. **Preventive health care for children with genetic conditions - providing primary care medical home, 2nd edition.** Acta Paediatr. 2008 Jan;97(1):136.

## **BAKKER M**

Bakker MK, de Walle HE, de Jong-van den Berg LT. **Reply to Martínez-Frías and Rodríguez-Pinilla.** Birth Defects Res A Clin Mol Teratol. 2008 Jan 9 [Epub ahead of print].

Eurocat Northern Netherlands, Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

\* \* \*

Bakker MK, Kölling P, van den Berg PB, de Walle HE, de Jong van den Berg LT. **Increase in use of selective serotonin reuptake inhibitors in pregnancy during the last decade, a population-based cohort study from the Netherlands.** Br J Clin Pharmacol. 2008 Apr;65(4):600-6. Epub 2007 Oct 22.

EUROCAT registration of congenital anomalies, Department of Genetics, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands.

### **WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT:**

Recently, the use of selective serotonin reuptake inhibitors (SSRIs), particularly paroxetine, in pregnancy has been associated with an increased risk on specific birth defects or other adverse pregnancy outcomes. However, the extent of SSRI use in pregnancy is largely unknown.

### **WHAT THIS STUDY ADDS:**

In the last decade the use of SSRIs in the year preceding delivery has increased twofold. This increase runs parallel with the increase in use of SSRIs among women of fertile age. Paroxetine is one of the most commonly used SSRIs. Only recently have sufficient data become available on the use of paroxetine to detect moderate increased risks for specific malformations. The safety of SSRIs which are less frequently used is not yet established. Case-control birth defect-monitoring systems may be helpful in providing safety and risk estimates that become more precise as data accumulate for these drugs. AIMS: Recent case-control studies suggest a relationship between the use of selective serotonin reuptake inhibitors (SSRIs) and the occurrence of birth defects and other adverse pregnancy outcomes. The aim was to determine the extent of the use of SSRIs before and during pregnancy and its trend over the years 1995-2004 in the Netherlands. METHODS: The study was performed with data from a population-based prescription database. Within this database, women giving birth to a child between 1995 and 2004 were identified. The exposure rate and 95% confidence interval (CI) were calculated as the number of pregnancies per 1000 that were exposed to an SSRI in a defined period (per trimester or in the year preceding delivery). Exposure rates were calculated for 2-year periods: 1995/1996, 1997/1998, 1999/2000, 2001/2002 and 2003/2004. Trends in exposure rates were analysed using the chi(2) test for trend. RESULTS: Included were 14,902

pregnancies for which complete pharmacy records were available from 3 months before pregnancy until delivery. A total of 310 pregnancies were exposed to an SSRI in the year preceding delivery. The exposure rate increased from 12.2 (95% CI 7.0, 19.8) in 1995/1996 to 28.5 (95% CI 23.0, 34.9) in 2003/2004.

**CONCLUSION:** There has been a significant increase in the use of SSRIs among pregnant women in the Netherlands over the last 10 years, parallel with the increase in exposure in women of fertile age. In light of the recent warnings about the use of SSRIs in pregnancy, healthcare professionals should be careful in prescribing SSRIs to women planning a pregnancy.

\* \* \*

Bakker MK, de Walle HE, Dequito A, van den Berg PB, de Jong-van den Berg LT. **Selection of controls in case-control studies on maternal medication use and risk of birth defects.** Birth Defects Res A Clin Mol Teratol. 2007 Sep;79(9):652-6.

EUROCAT Registration of Congenital Anomalies, Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.  
m.k.bakker@medgen.umcg.nl

**BACKGROUND:** In case-control studies on teratogenic risks of maternal drug use during pregnancy, the use of normal or malformed controls may lead to recall-bias or selection bias. This can be avoided by using controls with a genetic disorder.

However, researchers are hesitant to use these as controls because it is unknown whether their selection is independent of exposure status. The aim of this study is to investigate whether first trimester drug use among mothers of children with genetic disorders is representative for the "general pregnant population".

**METHODS:** From a birth defects registry 565 mothers of infants with a genetic disorder born between 1998-2004 were selected (the "genetic population"). The first trimester exposure rate was calculated for prescription-only drugs as the number of exposed women per 100. By calculating the rate ratio (RR) and 95% CI, the exposure rates in the genetic population were compared with those in the "source population" obtained from a population-based prescription database and consisting of 10,870 mothers who gave birth to a child between 1998-2004.

**RESULTS:** The mean age at birth was 32.1 for the genetic population and 29.6 for the source population ( $p = .000$ ). In the genetic population, a higher use was found for antimigraine medication (RR = 2.7, 95% CI = 1.0-7.8) and for ovulation stimulants (RR = 1.6, 95% CI = 1.0-2.6). After adjustment for maternal age, the difference in use of ovulation stimulants disappeared.

**CONCLUSIONS:** Except for antimigraine medication, first trimester drug use among mothers of infants with genetic disorders is representative for the general pregnant population.

## BIANCHI F

Barisic I, Tokic V, Loane M, Bianchi F, Calzolari E, Garne E, Wellesley D, Dolk H; EUROCAT Working Group. **Descriptive epidemiology of Cornelia de Lange syndrome in Europe.** Am J Med Genet A. 2008 Jan 1;146(1):51-9.

Children's University Hospital Zagreb, Zagreb, Croatia. ingeborg.barisic@kdb.hr

Cornelia de Lange syndrome (CdLS) is a multiple congenital anomaly/mental retardation syndrome consisting of characteristic dysmorphic features, microcephaly, hypertrichosis, upper limb defects, growth retardation, developmental delay, and a variety of associated malformations. We present a population-based epidemiological study of the classical form of CdLS. The data were extracted from the database of European Surveillance of Congenital Anomalies (EUROCAT) database, a European network of birth defect registries which follow a standard methodology. Based on 23 years of epidemiologic monitoring (8,558,346 births in the 1980-2002 period), we found the prevalence of the classical form of CdLS to be 1.24/100,000 births or 1:81,000 births and estimated the overall CdLS prevalence at 1.6-2.2/100,000. Live born children accounted for 91.5% (97/106) of cases, fetal deaths 2.8% (3/106), and terminations of pregnancy following prenatal diagnosis 5.7% (6/106). The most frequent associated congenital malformations were limb defects (73.1%), congenital heart defects (45.6%), central nervous system malformations (40.2%), and cleft palate (21.7%). In the last 11 years, as much as 68% of cases with major malformations were not detected by routine prenatal US. Live born infants with CdLS have a high first week survival (91.4%). All patients were sporadic. Maternal and paternal age did not seem to be risk factors for CdLS. Almost 70% of patients, born after the 37<sup>th</sup> week

of gestation, weighed  $\leq 2,500$  g. Low birth weight correlated with a more severe phenotype. Severe limb anomalies were significantly more often present in males.

## **BOURNE D**

Sayed AR, Bourne D, Pattinson R, Nixon J, Henderson B. **Decline in the prevalence of neural tube defects following folic acid fortification and its cost-benefit in South Africa.** Birth Defects Res A Clin Mol Teratol. 2008 Mar 12 [Epub ahead of print]

School of Public Health and Family Medicine, University of Cape Town, South Africa.

**BACKGROUND:** In October 2003 South Africa embarked on a program of folic acid fortification of staple foods. We measured the change in prevalence of NTDs before and after fortification and assessed the cost benefit of this primary health care intervention.

**METHODS:** Since the beginning of 2002 an ecological study was conducted among 12 public hospitals in four provinces of South Africa. NTDs as well as other birth defect rates were reported before and after fortification. Mortality data were also collected from two independent sources.

**RESULTS:** This study shows a significant decline in the prevalence of NTDs following folic acid fortification in South Africa. A decline of 30.5% was observed, from 1.41 to 0.98 per 1,000 births (RR = 0.69; 95% CI: 0.49-0.98;  $p = .0379$ ). The cost benefit ratio in averting NTDs was 46 to 1. Spina bifida showed a significant decline of 41.6% compared to 10.9% for anencephaly. Additionally, oro-facial clefts showed no significant decline (5.7%). An independent perinatal mortality surveillance system also shows a significant decline (65.9%) in NTD perinatal deaths, and in NTD infant mortality (38.8%).

**CONCLUSIONS:** The decrease in NTD rates postfortification is consistent with decreases observed in other countries that have fortified their food supplies. This is the first time this has been observed in a predominantly African population. The economic benefit flowing from the prevention of NTDs greatly exceeds the costs of implementing folic acid fortification. Birth Defects Research (Part A), 2008.

## **BOWER C**

Barrett SL, Bower C, Hadlow NC. **Use of the combined first-trimester screen result and low PAPP-A to predict risk of adverse fetal outcomes.** Prenat Diagn. 2008 Jan;28(1):28-35.

Western Diagnostic Pathology, Symbion Health, Western Australia, Australia. sandieb@aapt.net.au

**OBJECTIVES:** To investigate associations between combined first-trimester screen result, pregnancy associated plasma protein-A (PAPP-A) level and adverse fetal outcomes in women.

**METHODS:** Pregnancy outcomes for 10,273 women participating in a community based first-trimester screening (FTS) programme in Western Australia were ascertained by record linkage to birth and birth defect databases. A first-trimester risk cut-off of  $\geq 1$  in 300 defined screen positive women.

**RESULTS:** Screen positive pregnancies were more likely to have Down syndrome and birth defects (chromosomal or nonchromosomal) than screen negative pregnancies. When birth defects were excluded, screen positive pregnancies were at increased risk of pregnancy loss, low birth weight and preterm birth. Pregnancies with low PAPP-A ( $< \text{or} = 0.3$  multiples of the median (MoM)) had higher risk of chromosomal abnormality, birth defect, preterm birth, low birth weight, or pregnancy loss, compared to those with PAPP-A  $> 0.3$  MoM. In pregnancies without birth defects, low PAPP-A was a stronger predictor of preterm birth, low birth weight or pregnancy loss than a screen positive result.

**CONCLUSIONS:** Women with positive screen or low PAPP-A were at increased risk for some adverse fetal outcomes. The sensitivity of these parameters was insufficient to support primary screening, but increased surveillance during pregnancy may be appropriate.

\* \* \*

Leonard H, Nassar N, Bourke J, Blair E, Mulroy S, de Klerk N, Bower C. **Relation between intrauterine growth and subsequent intellectual disability in a ten-year population cohort of children in Western Australia.** Am J Epidemiol. 2008 Jan 1;167(1):103-11. Epub 2007 Sep 26.

Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, West Perth, Australia. hleonard@ichr.uwa.edu.au

The authors investigated the association between intrauterine growth and intellectual disability (ID). The appropriateness of intrauterine growth was assessed using percentage of optimal birth weight, a measure that accounts for gestational age, maternal height, parity, and infant sex. Using population-based record linkage, singleton Caucasian and Aboriginal children born in Western Australia in 1983-1992 and alive in 2002 with ID of unknown cause (n = 2,625) were compared with children without ID (n = 217,252). The odds of ID increased with less-than-optimal intrauterine growth. In Caucasian children, after adjustment for sociodemographic factors, severe growth restriction was associated with development of mild-moderate ID among preterm births (<37 weeks) (odds ratio (OR) = 1.71, 95% confidence interval (CI): 1.06, 2.77) and term births (> or =37 weeks) (OR = 2.42, 95% CI: 1.88, 3.12) and with severe ID (OR = 4.79, 95% CI: 2.59, 8.83) among term births. Effects were similar among Aboriginal children. Severe growth restriction (OR = 3.2, 95% CI: 1.3, 7.9) and poor head growth (OR = 3.6, 95% CI: 1.4, 9.0) were independently associated with severe ID. Infants with excess intrauterine growth were more likely to be diagnosed with ID associated with autism spectrum disorder (OR = 2.36, 95% CI: 0.93, 6.03). These findings suggest that inappropriate intrauterine growth, less than or greater than optimal birth weight, is associated with development of ID.

\* \* \*

Peadon E, O'Leary C, Bower C, Elliott E. **Impacts of alcohol use in pregnancy--the role of the GP.** Aust Fam Physician. 2007 Nov;36(11):935-9.

The Children's Hospital at Westmead, New South Wales. elizabp5@chw.edu.au

**BACKGROUND:** Fetal alcohol syndrome (FAS) is a preventable cause of developmental delay and growth failure.

**OBJECTIVE:** This article discusses the clinical features of fetal alcohol spectrum disorders (FASD) and the role of the general practitioner in prevention and management.

**DISCUSSION:** Early diagnosis of and intervention for problems associated with FAS reduce adverse long term outcomes. Most health professionals have limited knowledge of FASD and lack confidence in the diagnosis and management of children with FASD. General practitioners have an important role in identifying women and children at risk of harm from alcohol and arranging referral for assessment and management when necessary. Educational materials for health professionals are currently under development.

\* \* \*

Zurynski YA, Peadon E, Bower C, Elliott EJ. **Impacts of national surveillance for uncommon conditions in childhood.** J Paediatr Child Health. 2007 Nov;43(11):724-31.

Australian Paediatric Surveillance Unit, The Children's Hospital at Westmead, Westmead, NSW, Australia. yvonnez@chw.edu.au

The Australian Paediatric Surveillance Unit (APSU) facilitates the conduct of national collaborative research that is consistent with national health priorities, has potential to impact on public health, and addresses gaps in knowledge. Since 1993 paediatricians and other child health specialists have contributed monthly data on rare childhood conditions to the APSU. Over 40 conditions, including infectious diseases, injuries, vaccine-preventable diseases and genetic disorders have been studied. Information on epidemiology, frequency, diagnosis, management and short-term outcomes of these conditions is collected and provides evidence to support changes to clinical practice, prevention policy and allocation of health resources. In this review we give examples of the value of information gathered through the APSU surveillance system in the last 14 years.

\* \* \*

O'Leary CM, Bower C, Knuiman M, Stanley FJ. **Changing risks of stillbirth and neonatal mortality associated with maternal age in Western Australia 1984-2003.** Paediatr Perinat Epidemiol. 2007 Nov;21(6):541-9.

Division of Population Sciences, Telethon Institute for Child Health Research, Australia. colleeno@ichr.edu.au

There has been a trend over the past two decades in some Western countries for women to delay childbearing, a factor associated with an increased risk of perinatal mortality (stillbirth and neonatal death).

While the rates of stillbirth and neonatal mortality have improved in some countries, it has not been established whether maternal age remains a risk factor for perinatal mortality in Australia. The Western Australian Maternal and Child Health Research Database (MCHRDB) was used to examine the effect of maternal age on perinatal death in the periods 1984-93 and 1994-2003 after adjustment for parity and sociodemographic factors. Stillbirths and neonatal deaths were analysed separately. The crude rate of stillbirth has shown little change over the 20 years examined remaining at around 7.5 per 1000 total births, while the rate of neonatal death has decreased steadily from 5.4 per 1000 livebirths in 1984 to 2.0 in 2003. Older maternal age remains a risk factor for stillbirth but the relative risk has declined. After adjustment for parity and sociodemographic factors the relative risk of stillbirth for a woman aged over 40 years (compared with a woman aged 25-29 years) decreased from 2.6 in the period 1984-93, to 1.9 in the period 1994-2003. The increased risk of stillbirth associated with teenage mothers was fully explained by sociodemographic factors in both time periods. No increased risk of neonatal death was evident in the recent period 1994-2003 for teenage or older mothers after adjustment for parity and sociodemographic factors. In spite of some improvements over the past 20 years, women 30 years of age and older continue to be at increased risk of stillbirth. The risk of neonatal death is no longer associated with increased maternal age; however, the small number of cases in the older maternal age groups may be a result of the increased prevalence of antenatal screening and terminations for birth defects.

## **CANFIELD MA**

Ethen MK, Ramadhani TA, Scheuerle AE, Canfield MA, Wyszynski DF, Druschel CM, Romitti PA; National Birth Defects Prevention Study. **Alcohol Consumption by Women Before and During Pregnancy.** *Matern Child Health J.* 2008 Mar 4 [Epub ahead of print]

Texas Department of State Health Services, Birth Defects Epidemiology and Surveillance Branch, 1100 West 49th Street, Rm T-707 (mail code 1964), Austin, TX, 78756, USA, mary.ethen@dshs.state.tx.us.

**Objectives** To determine the prevalence, patterns, and predictors of alcohol consumption prior to and during various intervals of pregnancy in the U.S. **Methods** Alcohol-related, pregnancy-related, and demographic data were derived from computer-assisted telephone interviews with 4,088 randomly selected control mothers from the National Birth Defects Prevention Study who delivered live born infants without birth defects during 1997-2002. Alcohol consumption rates and crude and adjusted odds ratios (OR) were calculated. Results 30.3% of all women reported drinking alcohol at some time during pregnancy, of which 8.3% reported binge drinking (4+ drinks on one occasion). Drinking rates declined considerably after the first month of pregnancy, during which 22.5% of women reported drinking, although 2.7% of women reported drinking during all trimesters of pregnancy and 7.9% reported drinking during the 3rd trimester. Pre-pregnancy binge drinking was a strong predictor of both drinking during pregnancy (adjusted OR = 8.52, 95% CI = 6.67-10.88) and binge drinking during pregnancy (adjusted OR = 36.02, 95% CI = 24.63-52.69). Other characteristics associated with both any drinking and binge drinking during pregnancy were non-Hispanic white race/ethnicity, cigarette smoking during pregnancy, and having an unintended pregnancy. **Conclusions** Our study revealed that drinking during pregnancy is fairly common, three times the levels reported in surveys that ask only about drinking during the month before the survey. Women who binge drink before pregnancy are at particular risk for drinking after becoming pregnant. Sexually active women of childbearing ages who drink alcohol should be advised to use reliable methods to prevent pregnancy, plan their pregnancies, and stop drinking before becoming pregnant.

\* \* \*

Ethen MK, Canfield MA, Trevino J. **Pilot test of prenatal surveillance for birth defects in South Texas.** *Birth Defects Res A Clin Mol Teratol.* 2007 Nov;79(11):788-91.

Texas Center for Birth Defects Research and Prevention, Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, Texas, USA. mary.ethen@dshs.state.tx.us

**BACKGROUND:** The Texas Birth Defects Registry (TBDR) does not access prenatal diagnostic facilities to ascertain cases. Objectives of the study were to determine how many cases may be missing from the registry as a result, and to assess the feasibility and utility of prenatal surveillance for birth defects, through a pilot test in one region of Texas.

**METHODS:** A trained abstractor reviewed medical records of all patients with abnormal ultrasound findings during 2004 in all prenatal diagnostic facilities in Texas Health Region 11 (n = 6 facilities). When birth defects

were prenatally detected, demographic and diagnostic data were abstracted. Prenatal abstractions were matched to cases in the TBDR. Those that did not match to registry cases were matched to vital records to determine where and when the pregnancy ended; delivery hospital medical records were reviewed for these cases.

RESULTS: Approximately 760 patient charts were reviewed at prenatal diagnostic facilities and 365 were abstracted. Of these, 165 (45%) matched to cases in the TBDR. Delivery medical records were located and reviewed for 177 prenatal abstractions, with 170 (47%) indicating at delivery no defects monitored by the registry. Delivery records for one (0.3%) prenatal abstraction were not found by the hospital. Date and place of delivery were unknown for 22 (6%) prenatal abstractions. Only eight additional infants and fetuses (one twin pair) eligible for the registry were identified.

CONCLUSIONS:

For Texas Health Service Region 11, it is not necessary to conduct surveillance in prenatal diagnostic facilities, and to do so would be very labor-intensive.

\* \* \*

Case AP, Ramadhani TA, Canfield MA, Wicklund CA. **Awareness and attitudes regarding prenatal testing among Texas women of childbearing age.** J Genet Couns. 2007 Oct;16(5):655-61. Epub 2007 Aug 3.

Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX 78756, USA. amy.case@dshs.state.tx.us

Despite increased visibility and availability of prenatal testing procedures, very little is known about the attitudes among the populace toward these procedures. Using a computer assisted telephone interview of pregnant and non-pregnant women of childbearing age we analyze awareness and attitudes regarding prenatal tests among a diverse group of women of childbearing age in Texas. We also examine maternal characteristics associated with awareness and the willingness to undergo these procedures. While 89% were aware that such tests are available, younger, black and less educated women were less likely to know about prenatal tests for birth defects. Seventy-two percent of respondents said they would want their baby tested while Hispanic and black women were significantly more likely to express an interest than non-Hispanic whites. This study demonstrates the variability of knowledge and beliefs and confirms the importance of taking time to understand an individual's personal beliefs, knowledge and attitudes about prenatal diagnosis.

## CASTILLA EE

Bloch M, Althabe F, Onyamboko M, Kaseba-Sata C, Castilla EE, Freire S, Garces AL, Parida S, Goudar SS, Kadir MM, Goco N, Thornberry J, Daniels M, Bartz J, Hartwell T, Moss N, Goldenberg R. **Tobacco Use and Secondhand Smoke Exposure During Pregnancy: An Investigative Survey of Women in 9 Developing Nations.** Am J Public Health. 2008 Feb 28 [Epub ahead of print]

Objectives.

We examined pregnant women's use of cigarettes and other tobacco products and the exposure of pregnant women and their young children to secondhand smoke (SHS) in 9 nations in Latin America, Asia, and Africa. Methods. Face-to-face surveys were administered to 7961 pregnant women (more than 700 per site) between October 2004 and September 2005. Results. At all Latin American sites, pregnant women commonly reported that they had ever tried cigarette smoking (range: 78.3% [Uruguay] to 35.0% [Guatemala]). The highest levels of current smoking were found in Uruguay (18.3%), Argentina (10.3%), and Brazil (6.1%). Experimentation with smokeless tobacco occurred in the Democratic Republic of the Congo and India; one third of all respondents in Orissa, India, were current smokeless tobacco users. SHS exposure was common: between 91.6% (Pakistan) and 17.1% (Democratic Republic of the Congo) of pregnant women reported that smoking was permitted in their home. Conclusions. Pregnant women's tobacco use and SHS exposure are current or emerging problems in several low- and middle-income nations, jeopardizing ongoing efforts to improve maternal and child health.

\* \* \*

Poletta FA, Castilla EE, Orioli IM, Lopez-Camelo JS. **Regional analysis on the occurrence of oral clefts in South America.** Am J Med Genet A. 2007 Dec 15;143(24):3216-27.

ECLAMC (Latin American Collaborative Study of Congenital Malformations) at CEMIC (Center for Medical Education and Clinical Research), Buenos Aires, Argentina.

The aim of this work was to search for unequal birth prevalence rates (BPRs) of cleft lip +/- cleft palate (CL/P), and cleft palate only (CPO), among different geographic areas in South America, and to analyze phenotypic characteristics and associated risk factors in each identified cluster. Included were 5,128 CL/P cases, 1,745 CPO cases, and 3,712 controls (like-sexed, non-malformed liveborn infant, born immediately after a malformed one, in the same hospital), over 4,199,630 consecutive births. They were ascertained between 1967 and 2004, in 190 maternity hospitals of the ECLAMC (Estudio Colaborativo Latinoamericano de Malformaciones Congénitas) network, in 102 cities of all 10 South American countries. Non-predefined geographical areas with significantly unusual cleft BPRs were identified with Kulldorf and Nagarwalla's spatial scan statistic, employing number of cases and births, and exact location of each hospital. Expected values were cleft BPRs registered for the entire ECLAMC hospital network. Syndromic and non-syndromic clefts were considered for cluster analysis, and phenotypic characterization, while only non-syndromic for risk factor analysis. Seven clusters for CL/P, and four for CPO, with unusual BPRs were identified. CL/P cases in high BPR areas were more severe than elsewhere in the sample, similar to a previous ECLAMC report on microtia. For CL/P, high BPR clusters were associated with high altitude above sea level, Amerindian ancestry, and low socioeconomic strata; low BPR clusters showed association with African Black ancestry. Advanced maternal age, a recognized risk factor for CPO, was also associated with the only identified geographic cluster for CPO.

\* \* \*

Orioli IM, Castilla EE. **Clinical epidemiologic study of holoprosencephaly in South America.** Am J Med Genet A. 2007 Dec 15;143(24):3088-99.

Estudo Colaborativo Latino Americano de Malformações Congênitas: ECLAMC at Departamento de Genética, Curso de Pós-Graduação em Genética, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil.

ECLAMC: Latin American Study of Congenital Malformations examined 4,157,224 births (1967-2000), detecting 370 newborns with suspected holoprosencephaly (HPE): 182 (49.2%) had only craniofacial defects; 99 (26.8%) had defects in other systems; (15.1%) had chromosomal anomalies; 5 (1.4%) had recognized syndromes; and 28 (7.6%) had isolated median cleft lip. The latter group was excluded from subsequent analyses because of epidemiological differences from the other groups.

The birth prevalence rate (BPR) of isolated HPE was homogeneous among the 11 sampled countries, increasing from 0.5/10,000 births to 1/10,000 births between 1967 and 2000, suggesting improved ascertainment, mainly after 1996. Microtia, cleft lip/palate, and microstomia were preferentially associated with HPE, but cleft palate only was not. Maternal diabetes was more prevalent in HPE than in controls when adding the isolated and associated groups (OR: 3.5; 95% CI: 0.9-16.2). Maternal flu was more prevalent in isolated HPE (OR: 3.6; 0.9-16.6) and in isolated plus associated HPE (OR: 2.8; 1.0-7.9) than in controls. A second series of better documented HPE cases, 179 in number (2.2/10,000), ascertained from 827,968 births occurring from 2000 to 2003, was used for phenotypic definition of cerebral and facial anomalies. In 83 of 174 HPE cases with specified cerebral defects, 40% were alobar, 43% were semilobar, and 17% were lobar. All cases of cyclopia, ethmocephaly, and cebocephaly were of the alobar or semilobar types. Female excess occurred in the total sample, but not within the subgroups themselves because of their small sample sizes. Neither alobar HPE nor cyclopia was associated with female predilection. Among the 174 HPE cases, 39% had neither oral clefting nor a severe dysmorphic face. Of facial phenotypes, 26% had cyclopia, ethmocephaly, or cebocephaly; 25% had premaxillary agenesis; and 10% had cleft lip and palate or cleft palate only. Cyclopia was not associated with oral clefts; 6 of 8 cases of ethmocephaly had cleft palate; 6 of 20 cases of cebocephaly had oral clefts; 4 of 20 cases had premaxillary agenesis; and 2 of 20 cases had cleft palate.

\* \* \*

Vieira AR, Cooper ME, Marazita ML, Orioli IM, Castilla EE. **Interferon regulatory factor 6 (IRF6) is associated with oral-facial cleft in individuals that originate in South America.** Am J Med Genet A. 2007 Sep 1;143(17):2075-8.

Department of Oral Biology and Center for Craniofacial and Dental Genetics, School of Dental Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania 15213, USA. arv11@dental.pitt.edu

\* \* \*

Schuler-Faccini L, Soares RC, de Sousa AC, Maximino C, Luna E, Schwartz IV, Waldman C, Castilla EE. **New cases of thalidomide embryopathy in Brazil**. Birth Defects Res A Clin Mol Teratol. 2007 Sep;79(9):671-2.

Federal University of Rio Grande do Sul Genetics Department; Fundacao Faculdade Federal de Ciencias Medicas, Clinical Genetics Department, Porto Alegre, Brazil. lavinia.faccini@ufrgs.br

Thalidomide is the best known human teratogen. Although withdrawn from the market in 1961, thalidomide was remarketed after 1965 in several countries, for the treatment of erythema nodosum leprosum. Thalidomide has a potent immunomodulatory property and has now a number of approved and off-label uses in dermatologic, oncologic, infectious and gastrointestinal conditions. In the U.S., FDA approved the use of thalidomide in 1998, but no cases of thalidomide embriophaty were registered after that. Since 1996 no new cases were reported in Latin America.

However, the Teratogen Information Service (TIS) Porto Alegre, recorded three new cases of thalidomide embriophaty born in Brazil since 2005. Considering that these three cases were not registered through a systematic surveillance system, but that came to our attention through a series of coincidental random events, it can be assumed that the actual occurrence of affected babies by thalidomide continues being as frequent as denounced ten years ago.

## COCCHI G

Cocchi G, Mastrocola M, Capelli M, Bastelli A, Vitali F, Corvaglia L. **Immunological patterns in young children with Down syndrome: is there a temporal trend?** Acta Paediatr. 2007 Oct;96(10):1479-82. Epub 2007 Aug 28.

Neonatology and Preventive Paediatric Department, University of Bologna, Bologna, Italy. guido.cocchi@unibo.it

Down syndrome is associated with an increased susceptibility to infections due to a deficiency of both specific and nonspecific immunity. AIM: The aim of the study was to analyze the temporal trends, if any, of some variables related to the immunological status of children affected by Down syndrome. METHODS: Heparinized blood samples were obtained by venipuncture in 30 children with Down syndrome, who were regularly followed in our department and analyzed for hematologic values, lymphocyte subpopulations, immunoglobulin dosage and zinc level. Results were compared with those of the normal population. RESULTS: In the first 5 years of life, we observed a progressive decrease in the medium values of lymphocytes, CD4(+) and plasma zinc levels, and an increase in CD8(+), immunoglobulin A, immunoglobulin G, immunoglobulin M and natural killer, but generally without exceeding the interval of normality. CONCLUSIONS: In Down syndrome children, the immune cellular status is similar to the normal population as far as white blood cell, lymphocyte, CD4(+), CD8(+), natural killer and immunoglobulins are concerned. Plasma level of zinc is normal from birth until 5 years but with a temporal trend of progressive reduction. This observation supports the hypothesis that a pharmacological supplementation may be necessary in Down syndrome children only after 5 years of age.

## CORREA A

Gilboa SM, Correa A, Alverson CJ. **Use of spline regression in an analysis of maternal prepregnancy body mass index and adverse birth outcomes: does it tell us more than we already know?** Ann Epidemiol. 2008 Mar;18(3):196-205. Epub 2008 Jan 16.

National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA.

PURPOSE: Categorical analyses of prepregnancy body mass index (BMI) have shown that maternal overweight and obesity are associated with adverse pregnancy outcomes. It is unclear whether further insight into these associations can be gained from spline regression. METHODS: We used spline regression to examine the relations between prepregnancy BMI and five adverse pregnancy outcomes in the Baltimore-

Washington Infant Study, a case-control study of congenital cardiac defects. Analyses included 3,226 singleton live-born control infants delivered 1981 through 1989. We modeled BMI using (a) traditional categories of underweight, average weight, overweight, and obese and (b) restricted quadratic splines. RESULTS: We confirmed that overweight status and obesity were associated with increased risk of macrosomia and large for gestational age. For these outcomes, splines provided detail about the associations at the ends of the BMI distribution and within the average BMI category. Spline analyses also showed that underweight status was associated with increased risk of preterm delivery.

CONCLUSIONS: Analyses of traditional categories of BMI provide good understanding of the associations with several adverse birth outcomes. For three outcomes, modeling with splines provided additional insight regarding dose-response relations within categories. Results suggest the need for further analyses of average BMI and adverse pregnancy outcomes.

\* \* \*

Caton AR, Bell EM, Druschel CM, Werler MM, Mitchell AA, Browne ML, McNutt LA, Romitti PA, Olney RS, Correa A; National Birth Defects Prevention Study. **Maternal hypertension, antihypertensive medication use, and the risk of severe hypospadias.** Birth Defects Res A Clin Mol Teratol. 2008 Jan;82(1):34-40.

Department of Epidemiology and Biostatistics, School of Public Health, University at Albany, Rensselaer, New York, USA. [arc05@health.state.ny.us](mailto:arc05@health.state.ny.us)

BACKGROUND: Hypertensive disorders occur in an estimated 5-10% of pregnancies, but few studies have examined birth defects in relation to high blood pressure and antihypertensive medication use. The objective of this study was to investigate the relationship between high blood pressure, antihypertensive medication use, and severe hypospadias.

METHODS: We used data from the National Birth Defects Prevention Study, a population-based, multicenter, case-control study of birth defects to assess risks for severe hypospadias in relation to self-reported high blood pressure and prenatal exposures to antihypertensive drugs in 758 male infants with severe hypospadias and 2,058 male controls born between 1997 and 2002. Logistic regression analyses estimated ORs and 95% CIs, adjusted for potential confounders.

RESULTS: We observed slight to moderate elevations in the risk of severe hypospadias for maternal untreated hypertension (adjusted OR 2.1; 95% CI: 1.6-2.9) and antihypertensive medication use during 1 month preconception through pregnancy month 4 (adjusted OR 1.4; 95% CI: 0.7-2.9). The association was strongest for subjects initiating medications after the fourth month (adjusted OR 5.0; 95% CI: 1.9-12.9).

CONCLUSIONS: We observed an association between hypertension, antihypertensive medication use, and the risk of severe hypospadias, particularly when medication use began late in pregnancy. Because hypospadias occurs in early pregnancy, the data suggest that hypertension and its morphologic/physiologic precursors play an etiologic role, perhaps via compromised uteroplacental perfusion.

\* \* \*

Caton AR, Bell EM, Druschel CM, Werler MM, Mitchell AA, Browne ML, McNutt LA, Romitti PA, Olney RS, Correa A; National Birth Defects Prevention Study. **Maternal hypertension, antihypertensive medication use, and the risk of severe hypospadias.** Birth Defects Res A Clin Mol Teratol. 2008 Jan;82(1):34-40.

Department of Epidemiology and Biostatistics, School of Public Health, University at Albany, Rensselaer, New York, USA. [arc05@health.state.ny.us](mailto:arc05@health.state.ny.us)

BACKGROUND: Hypertensive disorders occur in an estimated 5-10% of pregnancies, but few studies have examined birth defects in relation to high blood pressure and antihypertensive medication use. The objective of this study was to investigate the relationship between high blood pressure, antihypertensive medication use, and severe hypospadias.

METHODS: We used data from the National Birth Defects Prevention Study, a population-based, multicenter, case-control study of birth defects to assess risks for severe hypospadias in relation to self-reported high blood pressure and prenatal exposures to antihypertensive drugs in 758 male infants with severe hypospadias and 2,058 male controls born between 1997 and 2002. Logistic regression analyses estimated ORs and 95% CIs, adjusted for potential confounders.

RESULTS: We observed slight to moderate elevations in the risk of severe hypospadias for maternal untreated hypertension (adjusted OR 2.1; 95% CI: 1.6-2.9) and antihypertensive medication use during 1 month preconception through pregnancy month 4 (adjusted OR 1.4; 95% CI: 0.7-2.9). The association was strongest for subjects initiating medications after the fourth month (adjusted OR 5.0; 95% CI: 1.9-12.9).

CONCLUSIONS: We observed an association between hypertension, antihypertensive medication use, and the risk of severe hypospadias, particularly when medication use began late in pregnancy. Because hypospadias occurs in early pregnancy, the data suggest that hypertension and its morphologic/physiologic precursors play an etiologic role, perhaps via compromised uteroplacental perfusion.

\* \* \*

Shin M, Kucik JE, Correa A. **Causes of death and case fatality rates among infants with down syndrome in metropolitan Atlanta.** Birth Defects Res A Clin Mol Teratol. 2007 Nov;79(11):775-80.

Division of Birth Defects and Developmental Disabilities, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia, USA. mshin@cdc.gov

BACKGROUND: There is limited population-based information on the extent of underreporting of congenital heart defects (CHD) as a cause of death among infants with Down syndrome (DS) and on the variation in case fatality by presence of CHD and age at death.

METHODS: Using data from the Metropolitan Atlanta Congenital Defects Program (MACDP), we identified infants with DS born 1979-2003. We used data from Georgia death certificates and the National Death Index to determine vital status and identify causes of death. Using MACDP records as a reference, we calculated the sensitivity and positive predictive value of reports of CHD as any cause of death or contributing condition in death certificates. We calculated race-specific case fatality rate by infant's age at death and presence of CHD.

RESULTS: CHD was the most frequently reported cause of death from death certificates; however, a review of causes of death and birth defects data indicated a potentially greater impact of CHD among DS infant deaths than could be determined from the reported cause of death. The case fatality rate among infants with DS was significantly higher among blacks than whites, with the greatest racial disparity observed among infants without CHD who died in the post-neonatal period.

CONCLUSIONS: Efforts are needed to improve reporting of causes of death related to CHD among infants with DS that would allow for a clearer assessment of determinants of case fatality among DS infants and identification of possible ways to reduce the racial disparities.

\* \* \*

Besser LM, Shin M, Kucik JE, Correa A. **Prevalence of down syndrome among children and adolescents in metropolitan Atlanta.** Birth Defects Res A Clin Mol Teratol. 2007 Nov;79(11):765-74.

Division of Birth Defects and Developmental Disabilities, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia, USA.

BACKGROUND: Down syndrome (DS) prevalence estimates beyond infancy are needed to assess health service needs among those with DS.

METHODS: Children with DS born in metropolitan Atlanta from 1979 through 2003 were ascertained from a population-based birth defects registry. Vital status through 2003 was obtained using case records, vital records, and the National Death Index. Prevalence was calculated by dividing the children surviving with DS by the population derived from U.S. Census estimates. Variations in DS prevalence by race, heart defects, age, birth cohort, and time period were examined using Poisson regression.

RESULTS: In metropolitan Atlanta in 2003, there were 67 livebirths with DS (13.0 per 10,000 livebirths) and 738 0- to 19-year-olds surviving with DS (8.3 per 10,000 population). Over time, births to mothers 35 years and older and DS birth prevalence increased. Birth prevalence was higher among Whites, did not vary by sex, and was higher for infants without heart defects. DS prevalence among 0- to 14-year-olds increased over time ( $p < .05$ ). Within each 5 year birth cohort, prevalence decreased with age: this decrease was greater among Blacks than among Whites and among children with heart defects than among children without heart defects.

CONCLUSIONS: DS prevalence increased among livebirths and among young children. Further studies are warranted to determine whether health services are meeting the needs of an increasing number of children with DS.

\* \* \*

Riehle-Colarusso T, Strickland MJ, Reller MD, Mahle WT, Botto LD, Siffel C, Atkinson M, Correa A. **Improving the quality of surveillance data on congenital heart defects in the metropolitan Atlanta congenital defects program.** Birth Defects Res A Clin Mol Teratol. 2007 Nov;79(11):743-53.

National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia, USA. tj4@cdc.gov

**BACKGROUND:** One of the challenges in epidemiologic studies of congenital heart defects (CHDs) has been the lack of a current, standard nomenclature and classification system. Recently such a standard nomenclature became available from the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database. This study reports the classification of cases of CHDs in a birth defects surveillance database using modified STS nomenclature.

**METHODS:** Records of infants and fetuses in the Metropolitan Atlanta Congenital Defects Program delivered during 1968-2003 with CHD diagnoses were reviewed by a team of pediatric cardiologists. The cases were assigned one or more STS codes and subsequently grouped into successively broader levels of aggregation. Aggregation was based on presumed morphogenetically similar developmental mechanisms.

**RESULTS:** There were 12,639 cases reviewed, of which 89% had a single, primary STS code. Structural CHDs were found in 7,749 infants, while 4,890 were considered to have structurally normal hearts. Application of clinical CHD nomenclature improved the clinical accuracy of surveillance data by eliminating normal physiologic variants and obligatory shunt lesions. Classification also aggregated specific CHDs into groups appropriate for research and surveillance.

**CONCLUSIONS:** Application of a current, standard CHD nomenclature and classification system to cases in a birth defects surveillance database improves the specificity of cardiac diagnoses and allows for the development of a flexible case aggregation system for monitoring of CHD prevalence.

\* \* \*

Duke CW, Alverson CJ, Correa A. **Fetal death certificates as a source of surveillance data for stillbirths with birth defects.** Public Health Rep. 2007 Sep-Oct;122(5):664-9.

National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 1600 Clifton Rd., NE, Mailstop E-86, Atlanta, GA 30333, USA. cduke@cdc.gov

**OBJECTIVE:** We assessed fetal death certificates (FDCs) as a source of surveillance for stillbirths with birth defects by linkage with data from the Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based birth defects surveillance system.

**METHODS:** Stillbirths with defects in MACDP were identified from 1994 through 2002 and linked to FDCs. Sensitivity of FDCs for capturing stillbirths with defects was estimated, and predictors for a case being reported were assessed. Concordance for selected variables from each data source was evaluated.

**RESULTS:** Two hundred twenty-four of 257 stillbirths with birth defects in MACDP were linked to an FDC (linkage rate = 87.2%; 95% confidence interval [CI] 82.4, 91.0). Stillbirths of non-Hispanic black and Hispanic/other mothers were more likely to be issued an FDC (odds ratio [OR] = 5.6 [95% CI 1.9, 17.0] and 14.0 [95% CI 1.7, 114.0], respectively). Cases undergoing autopsy were more likely to be issued an FDC (OR = 3.2; 95% CI 1.1, 8.7). Performance of an amniocentesis was poorly recorded on FDCs. The sensitivity and positive predictive value of FDCs for selected classes of defects ranged from 10% to 70% and 25% to 93%, respectively.

**CONCLUSIONS:** Compared to FDCs, MACDP's active case identification improves the ascertainment of stillbirths with birth defects and the quality of certain recorded data.

\* \* \*

Romitti PA, Sun L, Honein MA, Reefhuis J, Correa A, Rasmussen SA. **Maternal periconceptional alcohol consumption and risk of orofacial clefts.** Am J Epidemiol. 2007 Oct 1;166(7):775-85. Epub 2007 Jul 3.

Department of Epidemiology, The University of Iowa, Iowa City, IA 52242, USA.

Using data from the National Birth Defects Prevention Study, the authors investigated the association between maternal reports of periconceptional alcohol consumption and clefting. Cases with a cleft lip, cleft palate, or both and unaffected controls delivered from 1997 through 2002 were ascertained. Interview reports of alcohol consumption were obtained from 1,749 (75.1%) case and 4,094 (68.2%) control mothers. Adjusted odds ratios and 95% confidence intervals were calculated to assess associations. Compared with

odds ratios for mothers with no reported consumption, those for mothers who consumed alcohol tended to be near to (cleft lip, cleft lip with cleft palate) or to exceed (cleft palate) unity. The odds ratios associated with binge drinking were elevated but did not demonstrate significantly increased risk for any phenotype; however, the odds ratios differed by the type of alcohol consumed, particularly for cleft palate (distilled spirits > wine > beer). These odds ratios were further increased among mothers with no reported folic acid intake. Although these findings suggest that the association between alcohol consumption and clefting might be most influenced by the type of beverage consumed and folic acid intake, they are preliminary and might reflect chance associations. Such findings need exploration in additional, large studies.

\* \* \*

Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A; National Birth Defects Prevention Study. **Seeking causes: Classifying and evaluating congenital heart defects in etiologic studies.** Birth Defects Res A Clin Mol Teratol. 2007 Oct;79(10):714-27.

Division of Medical Genetics, University of Utah, Salt Lake City, Utah 84132, USA. lorenzo.botto@hsc.edu

**BACKGROUND:** Classification and analysis of congenital heart defects (CHD) in etiologic studies is particularly challenging because of diversity of cardiac phenotypes and underlying developmental mechanisms. We describe an approach to classification for risk assessment of CHD based on developmental and epidemiologic considerations, and apply it to data from the National Birth Defect Prevention Study (NBDPS).

**METHODS:** The classification system incorporated the three dimensions of cardiac phenotype, cardiac complexity, and extracardiac anomalies. The system was designed to facilitate the assessment of simple isolated defects and common associations. A team with cardiologic expertise applied the system to a large sample from the NBDPS.

**RESULTS:** Of the 4,703 cases of CHDs in the NBDPS with birth years 1997 through 2002, 63.6% were simple, isolated cases. Specific associations of CHDs represented the majority of the remainder. The mapping strategy generated relatively large samples for most cardiac phenotypes and provided enough detail to isolate important subgroups of CHDs that may differ by etiology or mechanism.

**CONCLUSIONS:** Classification of CHDs that considers cardiac and extracardiac phenotypes is practically feasible, and yields manageable groups of well-characterized phenotypes. Although best suited for large studies, this approach to classification and analysis can be a flexible and powerful tool in many types of etiologic studies of heart defects.

\* \* \*

Duke CW, Alverson CJ, Correa A. **Fetal death certificates as a source of surveillance data for stillbirths with birth defects.** Public Health Rep. 2007 Sep-Oct;122(5):664-9.

National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 1600 Clifton Rd., NE, Mailstop E-86, Atlanta, GA 30333, USA. cduke@cdc.gov

**OBJECTIVE:** We assessed fetal death certificates (FDCs) as a source of surveillance for stillbirths with birth defects by linkage with data from the Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based birth defects surveillance system.

**METHODS:** Stillbirths with defects in MACDP were identified from 1994 through 2002 and linked to FDCs. Sensitivity of FDCs for capturing stillbirths with defects was estimated, and predictors for a case being reported were assessed. Concordance for selected variables from each data source was evaluated.

**RESULTS:** Two hundred twenty-four of 257 stillbirths with birth defects in MACDP were linked to an FDC (linkage rate = 87.2%; 95% confidence interval [CI] 82.4, 91.0). Stillbirths of non-Hispanic black and Hispanic/other mothers were more likely to be issued an FDC (odds ratio [OR] = 5.6 [95% CI 1.9, 17.0] and 14.0 [95% CI 1.7, 114.0], respectively). Cases undergoing autopsy were more likely to be issued an FDC (OR = 3.2; 95% CI 1.1, 8.7). Performance of an amniocentesis was poorly recorded on FDCs. The sensitivity and positive predictive value of FDCs for selected classes of defects ranged from 10% to 70% and 25% to 93%, respectively.

**CONCLUSIONS:** Compared to FDCs, MACDP's active case identification improves the ascertainment of stillbirths with birth defects and the quality of certain recorded data.

**DE VIGAN C**

de Vigan C, Khoshnood B, Cadio E, Vodovar V, Goffinet F. **[Prenatal diagnosis and prevalence of Down syndrome in the Parisian population, 2001-2005.]** [Article in French] *Gynecol Obstet Fertil.* 2008 Feb;36(2):146-50. Epub 2008 Feb 4.

Inserm UMR S149, IFR 69, unité de recherche épidémiologique en santé périnatale et santé des femmes, 75014, Paris, France; UPMC, université Paris-6, UMR S 149, 75005, Paris, France.

**OBJECTIVES:** To assess recent trends in the prevalence of Down syndrome and the proportion of cases with a prenatal diagnosis in the Parisian population.

**PATIENTS AND METHODS:** Four hundred and ninety-nine cases of Down syndrome were registered by the Paris Registry of Congenital Anomalies during the period 2001-2005. All cases with prenatal diagnosis were confirmed by cytogenetic examination. We analyzed trends in the total and live birth prevalence, the proportion of cases with a prenatal diagnosis and those with a pregnancy termination, as well as gestational age at diagnosis and termination. Analyses were stratified by maternal age and trends were tested by the Cochran-Armitage test and Anova.

**RESULTS:** Total prevalence of Down syndrome remained high (37.6 per 10,000 births, 95%CI 34.2-40.9) during this period because of advanced maternal age in Paris. The proportion of cases with a prenatal diagnosis (overall average 85.5%, 95% CI 81.8-88.1), and live birth prevalence of Down syndrome (7.1 per 10,000 live births, 95%CI 5.7-8.6) have remained fairly stable over time. The great majority of women (95% CI 95% 92.7-96.9) opted for a pregnancy termination following a prenatal diagnosis of Down syndrome. A trend towards an earlier gestational age at prenatal diagnosis was noted among women less than 30 years of age.

**DISCUSSION AND CONCLUSION:** It is important to continue to evaluate changes in the prenatal diagnosis of Down syndrome, notably in view of potential changes in screening practices and policies, and particularly if a first trimester strategy is adopted following recent recommendation by the "Haute Autorité de santé".

## **FELDKAMP M**

Byrne JL, Feldkamp ML. **Seven-week embryo with gastroschisis, multiple anomalies, and physiologic hernia suggests early onset of gastroschisis.** *Birth Defects Res A Clin Mol Teratol.* 2008 Mar 12 [Epub ahead of print]

Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, University of Utah Health Sciences Center, Salt Lake City, Utah.

Gastroschisis is an increasingly common birth defect involving the development of the ventral body wall. Extrusion of the bowel is usually paraumbilical, usually right sided, and associated anomalies are less common than in omphalocele. Recently, hypotheses regarding the timing of the typical gastroschisis defect have come into question. Unlike previous theories, Feldkamp et al. (2007) has postulated that gastroschisis occurs much earlier in development, before abdominal wall closure, which is completed by about 35 days postconception. We present a case of a spontaneously aborted dysmorphic embryo which exhibits features of the normal physiologic herniation of the midgut as well as gastrochisis. The co-existence of the abdominal wall defect in this abnormal embryo with the physiologic hernia supports the early development of this defect and also illustrates the causal heterogeneity of gastroschisis. *Birth Defects Research (Part A)*, 2008.

## **GATT M**

Savona-Ventura C, Gatt M, Zammit K, Grima S. **Twin pregnancy outcomes in the Maltese Islands.** *Int J Gynaecol Obstet.* 2007 Sep;98(3):255-6. Epub 2007 Jun 27.

Department of Obstetrics-Gynecology, Department of Health, Malta. [charles.savona-ventura@um.edu.mt](mailto:charles.savona-ventura@um.edu.mt)

## **HALLIDAY J**

Morley R, [Halliday JL](#), Donath SM. **A review of policies on alcohol use during pregnancy in Australia and other English-speaking countries, 2006. Comment.** Med J Aust. 2007 Sep 3;187(5):315; author reply 316.

Comment on:

Med J Aust. 2007 May 7;186(9):466-71.

\* \* \*

Nagle C, Gunn J, Bell R, Lewis S, Meiser B, Metcalfe S, Ukoumunne OC, Halliday J. **Use of a decision aid for prenatal testing of fetal abnormalities to improve women's informed decision making: a cluster randomised controlled trial [ISRCTN22532458].** BJOG. 2008 Feb;115(3):339-47.

Murdoch Childrens Research Institute, Parkville, Victoria, Australia. [cate.nagle@rwh.org.au](mailto:cate.nagle@rwh.org.au)

**OBJECTIVE:** To evaluate the effectiveness of a decision aid for prenatal testing of fetal abnormalities compared with a pamphlet in supporting women's decision making.

**DESIGN:** A cluster randomised controlled trial.

**SETTING:** Primary health care.

**POPULATION:** Women in early pregnancy consulting a GP.

**METHODS:** GPs were randomised to provide women with either a decision aid or a pamphlet. The decision aid was a 24-page booklet designed using the Ottawa Decision Framework. The pamphlet was an existing resource available in the trial setting.

**MAIN OUTCOME MEASURES:** Validated scales were used to measure the primary outcomes, informed choice and decisional conflict, and the secondary outcomes, anxiety, depression, attitudes to the pregnancy/fetus and acceptability of the resource. Outcomes were measured at 14 weeks of gestation from questionnaires that women completed and returned by post.

**FINDINGS:** Women in the intervention group were more likely to make an informed decision 76% (126/165) than those in the control group 65% (107/165) (adjusted OR 2.08; 95% CI 1.14-3.81). A greater proportion of women in the intervention group 88% (147/167) had a 'good' level of knowledge than those in the control group 72% (123/171) (adjusted OR 3.43; 95% CI 1.79-6.58). Mean (SD) decisional conflict scores were low in both groups, decision aid 1.71 (0.49), pamphlet 1.65 (0.55) (adjusted mean difference 0.10; 95% CI -0.02 to 0.22). There was no strong evidence of differences between the trial arms in the measures of psychological or acceptability outcomes.

**CONCLUSION:** A tailored prenatal testing decision aid plays an important role in improving women's knowledge of first and second trimester screening tests and assisting them to make decisions about screening and diagnostic tests that are consistent with their values.

\* \* \*

Collins VR, Muggli EE, Riley M, Palma S, [Halliday JL](#). **Is Down syndrome a disappearing birth defect? J** Pediatr. 2008 Jan;152(1):20-4, 24.e1. Epub 2007 Oct 22.

Comment in:

J Pediatr. 2008 Jan;152(1):3-4.

Public Health Genetics, Murdoch Childrens Research Institute, Royal Children's Hospital, Victoria, Australia. [veronica.collins@mcri.edu.au](mailto:veronica.collins@mcri.edu.au)

**OBJECTIVE:** To assess trends in the prevalence of Down syndrome (DS) from 1986 to 2004 in Victoria, Australia (population approximately 5 million).

**STUDY DESIGN:** The Victorian Birth Defects Register and the Prenatal Diagnosis Database were linked to ascertain all cases of DS. Total and birth prevalence estimates were calculated per year and presented as 3-year moving averages.

**RESULTS:** The total number of cases of DS increased from 113 in 1986 to 188 in 2004. The number of births declined over the first decade of the study, particularly in younger women, but total numbers have fluctuated between 45 and 60 births since 1996. In women under age 35 years, total prevalence was 10/10,000 until 1997 and then increased to 12.5/10,000. In older women, total prevalence increased from 70/10,000 to 90/10,000 in this time frame. Birth prevalence declined at first but remained relatively stable in the later years of the study. The proportion of cases diagnosed prenatally increased from 3% to 60% in younger women.

CONCLUSIONS: Our findings demonstrate the continuing need to devote resources to support individuals with DS and their families.

## LOWRY RB

De Wals P, Van Allen MI, Lowry RB, Evans JA, Van den Hof MC, Crowley M, Tairou F, Uh SH, Sibbald B, Zimmer P, Fernandez B, Lee NS, Niyonsenga T. **Impact of folic acid food fortification on the birth prevalence of lipomyelomeningocele in Canada.** Birth Defects Res A Clin Mol Teratol. 2008 Feb;82(2):106-9.

Department of Social and Preventive Medicine, Laval University, Quebec City, Qc, Canada. Philippe.Dewals@msp.ulaval.ca

BACKGROUND: Recent studies reported no reduction in the frequency of lipomeningomyelocele (LMMC) in Hawaii and Nova Scotia after the implementation of a folic acid food fortification policy in 1998, while a marked reduction in the prevalence of other NTDs was observed. This study was performed to assess the prevalence of LMMC in Canada in relation to the timing of food fortification.

METHODS: The study population included live births, stillbirths, and terminations of pregnancies because of fetal anomaly to women residing in seven Canadian provinces, from 1993 to 2002. In each province, the ascertainment of NTD cases relied on multiple sources, and in addition all medical charts were reviewed. The study period was divided into pre-, partial, and full fortification periods, based on results of red cell folate tests published in the literature.

RESULTS: A total of 86 LMMC cases were recorded among approximately 1.9 million live births. The average birth prevalence rate was 0.05/1,000, ranging from a minimum of 0.01/1,000 in 2002 to a maximum of 0.08/1,000 in 1999. There was statistical heterogeneity between years ( $p = .01$ ), but no pattern compatible with a decrease following fortification. Comparing the full fortification period with the prefortification period, there was a slight but not statistically significant decrease in LMMC birth prevalence.

CONCLUSIONS: LMMC seems to be pathogenically distinct from myelomeningocele and more studies are needed to understand the embryologic mechanisms leading to this condition, and the environmental and genetic factors involved in its etiology.

\* \* \*

Doherty ES, Lacbawan F, Hadley DW, Brewer C, Zalewski C, Kim HJ, Solomon B, Rosenbaum K, Domingo DL, Hart TC, Brooks BP, Immken L, Lowry RB, Kimonis V, Shanske AL, Jehee FS, Bueno MR, Knightly C, McDonald-McGinn D, Zackai EH, Muenke M. **Muenke syndrome (FGFR3-related craniosynostosis): expansion of the phenotype and review of the literature.** Am J Med Genet A. 2007 Dec 15;143(24):3204-15.

National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA.

Muenke syndrome is an autosomal dominant disorder characterized by coronal suture craniosynostosis, hearing loss, developmental delay, carpal and tarsal fusions, and the presence of the Pro250Arg mutation in the FGFR3 gene. Reduced penetrance and variable expressivity contribute to the wide spectrum of clinical findings in Muenke syndrome. To better define the clinical features of this syndrome, we initiated a study of the natural history of Muenke syndrome. To date, we have conducted a standardized evaluation of nine patients with a confirmed Pro250Arg mutation in FGFR3. We reviewed audiograms from an additional 13 patients with Muenke syndrome. A majority of the patients (95%) demonstrated a mild-to-moderate, low frequency sensorineural hearing loss. This pattern of hearing loss was not previously recognized as characteristic of Muenke syndrome.

We also report on feeding and swallowing difficulties in children with Muenke syndrome. Combining 312 reported cases of Muenke syndrome with data from the nine NIH patients, we found that females with the Pro250Arg mutation were significantly more likely to be reported with craniosynostosis than males ( $P < 0.01$ ). Based on our findings, we propose that the clinical management should include audiometric and developmental assessment in addition to standard clinical care and appropriate genetic counseling.

\* \* \*

Lowry RB, Baker E, Dixon J, Hinton L. **Familial mental retardation due to a cryptic subtelomeric translocation –del 14qter and dup 9qter (the Anyon phenotype)**. Clin Dysmorphol. 2007 Oct;16(4):223-9.

Department of Medical Genetics, Alberta Children's Hospital/University of Calgary, Calgary, Alberta, Canada. brian.lowry@calgaryhealthregion.ca

An example of familial mental retardation is described in which there is a distinctive phenotype. It consists of IQ in the 30-50 range, microcephaly, short stature, narrow skull, prominent ears and nose and a cryptic subtelomeric translocation resulting in del 14qter and dup 9qter. Variable features include congenital heart disease, peripheral neuropathy and epilepsy. The phenotype was described in 1965 by Anyon.

## **MARTINEZ FRIAS ML**

Martínez-Frías ML, Rodríguez-Pinilla E. **Problem of using cases with genetic anomalies as a reference group in case-control studies on drug use and birth defects**. Birth Defects Res A Clin Mol Teratol. 2008 Jan 9;82(3):173-174 [Epub ahead of print]

Departamento de Farmacología, Facultad de Medicina, Universidad Complutense, Madrid, Spain.

\* \* \*

Martínez-Frías ML, Bermejo E, Rodríguez-Pinilla E, Prieto D; EC EMC Working Group. **Does single umbilical artery (SUA) predict any type of congenital defect? Clinical-epidemiological analysis of a large consecutive series of malformed infants**. Am J Med Genet A. 2008 Jan 1;146(1):15-25.

EC EMC, Centro de Investigación sobre Anomalías Congénitas (CIAC), del Instituto de Salud Carlos III, Madrid, Spain. mlmartinez.frias@isciii.es

Most studies associating different types of malformations with the presence of a single umbilical artery (SUA) are based on small and selected series. Here, we present the results of a study aimed at identifying the most frequent, and the most specific anomalies related to SUA. We analyzed 19,909 consecutive newborn infants with congenital malformations, from the Spanish Collaborative Study of Congenital Malformations (EC EMC). To estimate the specificity of the relationship of different congenital defects with SUA, we calculated their relative frequencies (RF) by dividing their frequency in infants with SUA by the corresponding frequency in newborn infants without SUA. Using the different levels of the EC EMC coding system, we calculated the RFs in three steps: (a) a group of individual congenital defects, (b) different groups of malformed infants, and (c) each individual malformation by its clinical presentation in some of the studied groups of malformed infants. The defects most specifically associated with SUA were bilateral renal agenesis and imperforate anus, followed by unilateral renal agenesis, and vertebral defects, the RF of which indicated that they were between 7.99 and 9.93 times more frequent among malformed infants with SUA than among malformed infants without SUA. However, these defects were not as frequent in the group of infants with SUA, as cardiovascular anomalies.

Regarding the association of SUA in the groups of malformed infants, the most specific groups were body stalk defects and sirenómelia. Finally, we analyzed the association of the individual defects by different groups of malformed infants in order to identify if the individual defects are associated with SUA in any type of clinical presentation, and in relation to some groups of infants with genetic disorders. The results, together with the embryonic development of the umbilical cord, strongly suggest that not all cases of SUA have the same cause, and that all previously suggested mechanisms may be possible but with different frequencies.

\* \* \*

Frías JL, Frías JP, Frías PA, Martínez-Frías ML. **Infrequently studied congenital anomalies as clues to the diagnosis of maternal diabetes mellitus**. Am J Med Genet A. 2007 Dec 15;143(24):2904-9.

Department of Pediatrics, University of South Florida, Tampa, Florida, USA. jlfrias@comcast.net

The aim of this study was to identify congenital anomalies (CA) among infants of women with diabetes mellitus (DM) that, even though infrequent or infrequently reported, may suggest diabetic teratogenesis. Using 1976-2005 data from the Spanish Collaborative Study of Congenital Malformations (ECEMC), we compared the frequency of selected CA among 130 infants with CA born to women with pregestational DM (PGDM) and 30,009 infants with CA whose mothers had normal glucose tolerance (NGT). To identify which CA were not only significantly more frequent among infants of mothers with PGDM, but also more specific, we calculated the quotient of their frequencies (frequency ratio: FR). The same analysis was made using data from 927 infants of mothers with gestational DM (GDM). Among the studied defects, several were statistically significantly more frequent among infants of PGDM mothers than among infants of mothers with NGT, although the specificity of their association with DM varied, as indicated by the values of the FR. These included: anorectal atresia/stenosis (FR = 2.81; P = 0.03), hallucal polydactyly (FR = 3.62; P = 0.002), heterotaxy (FR = 5.70; P = 0.049), hypertrophic cardiomyopathy (HCM) (FR = 61.60; P = 0.000000), multicystic dysplastic kidneys (MDK) (FR = 5.13; P = 0.0002), and thymus aplasia/hypoplasia (FR = 29.62; P = 0.000001). The only CA significantly more frequent among infants of women with GDM were HCM (FR = 8.60; P = 0.002) and MDK (FR = 1.80; P = 0.01).

Our results suggest that maternal PGDM should be suspected in children with hallucal polydactyly, anorectal atresia/stenosis, heterotaxy, or aplasia/hypoplasia of the thymus. The presence of transient HCM or MDK in a newborn suggests maternal PGDM or GDM. These observations are important in view of the increasing worldwide frequency of DM and the high proportion of individuals with DM in whom the condition remains undiagnosed.

## **MERLOB P**

Kaplan M, Merlob P, Regev R. **Israel guidelines for the management of neonatal hyperbilirubinemia and prevention of kernicterus.** J Perinatol. 2008 Mar 6 [Epub ahead of print]

Department of Neonatology, Shaare Zedek Medical Center, Faculty of Medicine of the Hebrew University, Jerusalem, Israel.

Despite publication of guidelines for the prevention and management of hyperbilirubinemia in term and late-preterm newborn infants, kernicterus, although rare, continues to occur. Guidelines written for use in one country may not always be universally appropriate. Bearing this in mind, a committee appointed by the Israel Neonatal Society has formulated a set of guidelines, based on those of the American Academy of Pediatrics (2004), but adapted to the realities of the Israeli scene. The guidelines include methods of surveillance of jaundice, prediction of jaundice, assessment of risk factors, discharge planning and post-discharge follow-up, in addition to therapeutic guidelines including indications for phototherapy, exchange transfusion and the use of intravenous immune globulin. Availability of these guidelines to the international community may offer direction to physicians of other countries who may be setting up guidelines for use in their own communities. Journal of Perinatology advance online publication, 6 March 2008; doi:10.1038/jp.2008.20.

\* \* \*

Basel-Vanagaite L, Kornreich L, Schiller O, Yacobovich J, Merlob P. **Yunis-Varon syndrome: further delineation of the phenotype.** Am J Med Genet A. 2008 Feb 15;146(4):532-7.

Department of Medical Genetics, Schneider Children's Medical Center of Israel and Rabin Medical Center, Beilinson Campus, Petah Tikva, Israel. basel@post.tau.ac.il

Yunis-Varon syndrome (YVS) is a rare autosomal recessive condition characterized by limb defects, ossification defects, generalized hypotrichosis and, frequently, a severe neonatal course. The molecular basis is unknown. We report on a newborn infant with previously undescribed findings, including hydrops fetalis, primary pulmonary hypertension and unusually severe abnormalities of toes. We review clinical data on 22 published cases in order to delineate the phenotype of this condition. Clinical recommendations for prenatal and postnatal evaluation of patients and fetuses at risk are discussed.

\* \* \*

Amir A, Merlob P, Linder N, Sirota L, Klinger G. **Mortality of full-term infants during the first month of life in a tertiary care hospital.** J Perinatol. 2007 Oct;27(10):620-2. Epub 2007 Aug 23.

Department of Neonatal Intensive Care, Schneider Children's Medical Center of Israel, Petah Tiqva, Israel.

**OBJECTIVE:** The neonatal mortality rate is disproportionately influenced by preterm infants and does not reflect the rate in full-term infants. Our objectives were to estimate the full-term neonatal mortality rate and to identify causes of death in full-term infants during the first month of life.

**STUDY DESIGN:** A retrospective study of full-term infant deaths during a 6-year period from 2000 to 2005, in a tertiary medical center.

**RESULT:** During the study period there were 44,703 full-term births and 31 deaths, representing a mortality rate of 0.69 per 1,000 live births. The main cause of death was congenital anomalies (64.5%), specifically cardiac anomalies. Other causes were chromosomal anomalies or syndromes (12.9%), labor complications (12.9%), infections (3.2%), congenital diseases (3.2%) and metabolic disorders (3.2%).

**CONCLUSION:** The mortality rate of full-term infants may be lower than previous estimates. Efforts aimed at decreasing mortality among full-term infants should focus on prenatal diagnosis.

### **SCARANO G**

Della Monica M, Lonardo F, Faravelli F, Pierluigi M, Luquetti DV, De Gregori M, Zuffardi O, Scarano G. **A case of autism with an interstitial 1q deletion (1q23.3-24.2) and a de novo translocation of chromosomes 1q and 5q.** Am J Med Genet A. 2007 Nov 15;143(22):2733-7.

Medical Genetics Department, Gaetano Rummo Hospital, Benevento, Italy.

Chromosomal abnormalities may cause autism by disrupting a gene or by providing a permissive genetic environment for mutations elsewhere in the genome to become expressed as autism. We report here on a patient with an apparently balanced de novo translocation of chromosomes 1q and 5q. He presented with minor dysmorphic features and renal malformations, mental retardation, and autism. Further characterization of the chromosomal rearrangement by FISH revealed a deletion in chromosome 1 from q23.3 to q24.2 corresponding to a region of rising interest in the research of autism susceptibility genes. The array-CGH technique gave better resolution of the breakpoints and the size of the deletion was calculated to be 4.97 Mb.

### **SULLIVAN E**

Tracy SK, Dahlen H, Tracy MB, Laws P, Sullivan E. **Reply: perinatal outcomes in birth centers.** Birth. 2008 Mar;35(1):86.

\* \* \*

Pollock W, Sullivan E, Nelson S, King J. **Capacity to monitor severe maternal morbidity in Australia.** Aust N Z J Obstet Gynaecol. 2008 Feb;48(1):17-25.

School of Nursing, The University of Melbourne, Carlton, Victoria, and AIHW National Advisory Committee on Maternal Mortality, Randwick, New South Wales, Australia.

Maternal mortality has traditionally been the key element in the monitoring of maternal health and adequacy of obstetric services in Australia and around the world. In developed countries, the ability of maternal mortality to serve this purpose is reduced because of the rarity of maternal mortality, reflected in very low maternal mortality ratios. Internationally, there has been increasing interest in severe maternal morbidity as an indicator to monitor maternal health and maternity services. The aim of this paper is to critically examine the capacity to measure and monitor maternal morbidity in Australia. There is a paucity of reliable maternal morbidity data in Australia; Australia is lagging behind peer countries that are endeavouring to monitor severe maternal morbidity. Dedicated efforts and adequate resources are needed in order to monitor severe maternal morbidity in Australia.

\* \* \*

Tracy SK, Tracy MB, Sullivan E. **Admission of term infants to neonatal intensive care: a population-based study.** Birth. 2007 Dec;34(4):301-7.

Women's Health Nursing and Midwifery, Royal Hospital for Women, Sydney, New South Wales, Australia.

**BACKGROUND:** Neonatal intensive care and special care nurseries provide a level of care that is both high in cost and low in volume. The aim of our study was to determine the rate of admission of term babies to neonatal intensive care in association with each method of giving birth among low-risk women.

**METHODS:** We examined the records of 1,001,249 women who gave birth in Australia during 1999 to 2002 using data from the National Perinatal Data Collection. Among low-risk women, we calculated the adjusted odds of admission to neonatal intensive care at term separated for each week of gestational age between 37 and 41 completed weeks. We also calculated the odds of admission to neonatal intensive care in association with cesarean section before or after the onset of labor, and vacuum or instrumental birth compared with unassisted vaginal birth at 40 weeks' gestation.

**RESULTS:** The overall rate of admission to neonatal intensive care of term babies was 8.9 percent for primiparas and 6.3 percent for multiparas. After a cesarean section before the onset of labor, the adjusted odds of admission among low-risk primiparas at 37 weeks' gestation were 12.08 (99% CI 8.64-16.89); at 38 weeks, 7.49 (99% CI 5.54-10.11); and at 39 weeks, 2.80 (99% CI 2.02-3.88). At 41 weeks, the adjusted odds were not significantly higher than those at 40 weeks' gestation. Among low-risk multiparas who had a cesarean section before the onset of labor, the adjusted odds of admission to neonatal intensive care at 37 weeks' gestation were 15.40 (99% CI 12.87-18.43); at 38 weeks, 12.13 (99% CI 10.37-14.19); and at 39 weeks, 5.09 (99% CI 4.31-6.00). At 41 weeks' gestation, the adjusted odds of admission were significantly lower than those at 40 weeks (AOR 0.64, 99% CI 0.47-0.88). Babies born after any operative method of birth were at increased odds of being admitted to neonatal intensive care compared with those born after unassisted vaginal birth at 40 weeks' gestation.

**CONCLUSIONS:** The adjusted odds of admission to neonatal intensive care for babies of low-risk women were increased after birth at 37 weeks' gestation. In a climate of rising cesarean sections, this information is important to women who may be considering elective procedures.

\* \* \*

Barnes D, Linton JL, Sullivan E, Bagley A, Oeffinger D, Abel M, Damiano D, Gorton G, Nicholson D, Romness M, Rogers S, Tylkowski C. **Pediatric outcomes data collection instrument scores in ambulatory children with cerebral palsy: an analysis by age groups and severity level.** J Pediatr Orthop. 2008 Jan-Feb;28(1):97-102.

Shriners Hospital for Children, Houston, TX 77030, USA. dbarnes@shrinenet.org

**BACKGROUND:** The Pediatric Outcomes Data Collection Instrument (PODCI) was developed in 1994 as a patient-based tool for use across a broad age range and wide array of musculoskeletal disorders, including children with cerebral palsy (CP). The purpose of this study was to establish means and SDs of the Parent PODCI measures by age groups and Gross Motor Function Classification System (GMFCS) levels for ambulatory children with CP.

**METHODS:** This instrument was one of several studied in a prospective, multicenter project of ambulatory patients with CP between the aged 4 and 18 years and GMFCS levels I through III. Participants included 338 boys and 221 girls at a mean age of 11.1 years, with 370 diplegic, 162 hemiplegic, and 27 quadriplegic. Both baseline and follow-up data sets of the completed Parent PODCI responses were statistically analyzed.

**RESULTS:** Age was identified as a significant predictor of the PODCI measures of Upper Extremity Function, Transfers and Basic Mobility, Global Function, and Happiness With Physical Condition. Gross Motor Function Classification System levels was a significant predictor of Transfers and Basic Mobility, Sports and Physical Function, and Global Function. Pattern of involvement, sex, and prior orthopaedic surgery were not statistically significant predictors for any of the Parent PODCI measures. Mean and SD scores were calculated for age groups stratified by GMFCS levels. Analysis of the follow-up data set validated the findings derived from the baseline data. Linear regression equations were derived, with age as a continuous variable and GMFCS levels as a categorical variable, to be used for Parent PODCI predicted scores. **CONCLUSIONS:** The results of this study provide clinicians and researchers with a set of Parent PODCI values for comparison to age- and severity-matched populations of ambulatory patients with CP.

\* \* \*

Scott AC, Kelly CH, Sullivan E. **Body mass index as a prognostic factor in development of infantile Blount disease.** Pediatr Orthop. 2007 Dec;27(8):921-5.

Shriners Hospital for Children, Houston, TX 77030, USA. ascott@shrinenet.org

**BACKGROUND:** Obesity has been associated with infantile Blount disease, yet no specific relationship has been established. The purpose of this study was to determine the relationship between body mass index (BMI) and the development of infantile Blount disease.

**METHODS:** A retrospective study was performed reviewing charts and radiographs of 69 consecutive children between 2 and 4 years old who presented during a 5-year period with the diagnosis of idiopathic genu varum.

**RESULTS:** Forty-nine of these children were noted to have physiological bowing that resolved. Twenty children were diagnosed with infantile Blount disease that required treatment. Logistic regression analysis compared the 2 groups and showed no statistical difference between their age at presentation and age of walking. An independent group Student t test showed a significant difference for body weight, BMI percentile, and weight for height percentile between children with physiological bowlegs and Blount disease. A highly significant difference between the 2 groups was shown in the patient's BMI, proximal tibial metaphyseal-diaphyseal angle, and tibial femoral angle. Based on these data, criteria were established for predicting Blount disease: a tibial metaphyseal-diaphyseal angle greater than or equal to 10 degrees and a BMI greater than or equal to 22. Using these criteria, this prediction method has a sensitivity of 95%, specificity of 100%, true-positive predictive value of 100%, and true-negative predictive value of 98%. **CONCLUSIONS:** The establishment of a statistically significant relationship between BMI and infantile Blount disease will be helpful to the orthopaedic surgeon in deciding which children would benefit from early treatment of bowlegs. In addition, nutritional counseling can be emphasized for those at risk.

\* \* \*

Tracy SK, Dahlen H, Caplice S, Laws P, Wang YA, Tracy MB, Sullivan E. **Birth centers in Australia: a national population-based study of perinatal mortality associated with giving birth in a birth center.** Birth. 2007 Sep;34(3):194-201.

Australian Institute of Health and Welfare National Perinatal Statistics Unit, School of Women's and Children's Health, University of New South Wales, Sydney, Australia.

**BACKGROUND:** Perinatal mortality is a rare outcome among babies born at term in developed countries after normal uncomplicated pregnancies; consequently, the numbers involved in large databases of routinely collected statistics provide a meaningful evaluation of these uncommon events. The National Perinatal Data Collection records the place of birth and information on the outcomes of pregnancy and childbirth for all women who give birth each year in Australia. Our objective was to describe the perinatal mortality associated with giving birth in "alongside hospital" birth centers in Australia during 1999 to 2002 using nationally collected data.

**METHODS:** This population-based study included all 1,001,249 women who gave birth in Australia during 1999 to 2002. Of these women, 21,800 (2.18%) gave birth in a birth center. Selected perinatal outcomes (including stillbirths and neonatal deaths) were described for the 4-year study period separately for first-time mothers and for women having a second or subsequent birth. A further comparison was made between deaths of low-risk term babies born in hospitals compared with deaths of term babies born in birth centers.

**RESULTS:** The total perinatal death rate attributed to birth centers was significantly lower than that attributed to hospitals (1.51/1,000 vs 10.03/1,000). The perinatal mortality rate among term births to primiparas in birth centers compared with term births among low-risk primiparas in hospitals was 1.4 versus 1.9 per 1,000; the perinatal mortality rate among term births to multiparas in birth centers compared with term births among low-risk multiparas in hospitals was 0.6 versus 1.6 per 1,000.

**CONCLUSIONS:** This study using Australian national data showed that the overall rate of perinatal mortality was lower in alongside hospital birth centers than in hospitals irrespective of the mother's parity.

## **SIFFEL C**

Riehle-Colarusso T, Strickland MJ, Reller MD, Mahle WT, Botto LD, Siffel C, Atkinson M, Correa A. **Improving the quality of surveillance data on congenital heart defects in the metropolitan Atlanta congenital defects program.** Birth Defects Res A Clin Mol Teratol. 2007 Nov;79(11):743-53.

National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia, USA. tj4@cdc.gov

**BACKGROUND:** One of the challenges in epidemiologic studies of congenital heart defects (CHDs) has been the lack of a current, standard nomenclature and classification system. Recently such a standard nomenclature became available from the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database. This study reports the classification of cases of CHDs in a birth defects surveillance database using modified STS nomenclature.

**METHODS:** Records of infants and fetuses in the Metropolitan Atlanta Congenital Defects Program delivered during 1968-2003 with CHD diagnoses were reviewed by a team of pediatric cardiologists. The cases were assigned one or more STS codes and subsequently grouped into successively broader levels of aggregation. Aggregation was based on presumed morphogenetically similar developmental mechanisms.

**RESULTS:** There were 12,639 cases reviewed, of which 89% had a single, primary STS code. Structural CHDs were found in 7,749 infants, while 4,890 were considered to have structurally normal hearts. Application of clinical CHD nomenclature improved the clinical accuracy of surveillance data by eliminating normal physiologic variants and obligatory shunt lesions. Classification also aggregated specific CHDs into groups appropriate for research and surveillance.

**CONCLUSIONS:** Application of a current, standard CHD nomenclature and classification system to cases in a birth defects surveillance database improves the specificity of cardiac diagnoses and allows for the development of a flexible case aggregation system for monitoring of CHD prevalence.

## TENCONI R

Concolino D, Rossi E, Strisciuglio P, Iembo MA, Giorda R, Ciccone R, Tenconi R, Zuffardi O. **Deletion of a 760 kb region at 4p16 determines the prenatal and postnatal growth retardation characteristic of Wolf-Hirschhorn syndrome.** J Med Genet. 2007 Oct;44(10):647-50.

**BACKGROUND:** Recently the genotype/phenotype map of Wolf-Hirschhorn syndrome (WHS) has been refined, using small 4p deletions covering or flanking the critical region in patients showing only some of the WHS malformations. Accordingly, prenatal-onset growth retardation and failure to thrive have been found to result from haploinsufficiency for a 4p gene located between 0.4 and 1.3 Mb, whereas microcephaly results from haploinsufficiency of at least two different 4p regions, one of 2.2-2.38 Mb and a second one of 1.9-1.28 Mb.

**METHODS AND RESULTS:** We defined the deletion size of a ring chromosome (r(4)) in a girl with prenatal onset growth retardation, severe failure to thrive and true microcephaly but without the WHS facial gestalt and mental retardation. A high-resolution comparative genome hybridisation array revealed a 760 kb 4p terminal deletion.

**CONCLUSIONS:** This case, together with a familial 4p deletion involving the distal 400 kb reported in normal women, may narrow the critical region for short stature on 4p to 360-760 kb. This region is also likely to contain a gene for microcephaly. "In silico" analysis of all genes within the critical region failed to reveal any strikingly suggestive expression pattern; all genes remain candidates for short stature and microcephaly.

## VOLLSET SE

Boyles AL, Wilcox AJ, Taylor JA, Meyer K, Fredriksen A, Ueland PM, Drevon CA, Vollset SE, Lie RT. **Folate and one-carbon metabolism gene polymorphisms and their associations with oral facial clefts.** Am J Med Genet A. 2008 Feb 15;146(4):440-9.

Epidemiology Branch, National Institute of Environmental Health Sciences/NIH, Durham, North Carolina 27709, USA. boylesa@niehs.nih.gov

Folate metabolism plays a critical role in embryonic development. Prenatal folate supplementation reduces the risk of neural tube defects and probably oral facial clefts. Previous studies of related metabolic genes have associated polymorphisms in cystathionine-beta-synthase (CBS) and 5,10-methylenetetrahydrofolate reductase (MTHFR) with cleft risk. We explored associations between genes related to one-carbon metabolism and clefts in a Norwegian population-based study that included 362 families with cleft lip with or without cleft palate (CL/P) and 191 families with cleft palate only (CPO). We previously showed a 39% reduction in risk of CL/P with folic acid supplementation in this population. In the present study we genotyped

12 polymorphisms in nine genes related to one-carbon metabolism and looked for associations of clefting risk with fetal polymorphisms, maternal polymorphisms, as well as parent-of-origin effects, using combined likelihood-ratio tests (LRT). We also stratified by maternal periconceptional intake of folic acid (>400 microg) to explore gene-exposure interactions. We found a reduced risk of CL/P with mothers who carried the CBS C699T variant (rs234706); relative risk was 0.94 with one copy of the T allele (95% CI 0.63-1.4) and 0.50 (95% CI 0.26-0.96) with two copies (P = 0.008). We found no evidence of interaction of this variant with folate status. We saw no evidence of risk from the MTHFR C677T variant (rs1801133) either overall or after stratifying by maternal folate intake. No associations were found between any of the polymorphisms and CPO. Genetic variations in the nine metabolic genes examined here do not confer a substantial degree of risk for clefts.

\* \* \*

Nilsen RM, Vollset SE, Rasmussen SA, Ueland PM, Daltveit AK. **Folic Acid and Multivitamin Supplement Use and Risk of Placental Abruption: A Population-based Registry Study.** Am J Epidemiol. 2008 Jan 10 [Epub ahead of print]

Section for Epidemiology and Medical Statistics, Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway.

The authors investigated a possible association of supplemental folic acid and multivitamin use with placental abruption by using data on 280,127 singleton deliveries recorded in 1999-2004 in the population-based Medical Birth Registry of Norway. Odds ratios, adjusted for maternal age, marital status, parity, smoking, pregestational diabetes, and chronic hypertension, were estimated with generalized estimating equations for logistic regression models. Use of folic acid and/or multivitamin supplements before or any time during pregnancy was reported for 36.4% of the abruptions (0.38% of deliveries) and 44.4% of the nonabruptions. Compared with no use, any supplement use was associated with a 26% risk reduction of placental abruption (adjusted odds ratio = 0.74, 95% confidence interval: 0.65, 0.84). Women who had taken folic acid alone had an adjusted odds ratio of 0.81 (95% confidence interval: 0.68, 0.98) for abruption, whereas multivitamin users had an adjusted odds ratio of 0.72 (95% confidence interval: 0.57, 0.91), relative to supplement nonusers. The strongest risk reduction was found for those who had taken both folic acid and multivitamin supplements (adjusted odds ratio = 0.68, 95% confidence interval: 0.56, 0.83). These data suggest that folic acid and other vitamin supplementation during pregnancy may be associated with reduced risk of placental abruption.