

# Papers published by Members of the International Clearinghouse for Birth Defects Surveillance and Research and appeared in the Medline in the period October 2008 - March 2009

## Australia: National - SULLIVAN E

Wang YA, Sullivan EA, Healy DL, Black DA.

**Perinatal outcomes after assisted reproductive technology treatment in Australia and New Zealand: single versus double embryo transfer.**

Med J Aust. 2009 Mar 2; 190(5):234-7.

Perinatal and Reproductive Epidemiology Research Unit, University of New South Wales, Sydney, NSW, Australia. alex.wang@unsw.edu.au.

**OBJECTIVE:** To compare the perinatal outcomes of babies conceived by single embryo transfer (SET) with those conceived by double embryo transfer (DET).

**DESIGN, SETTING AND PARTICIPANTS:** A retrospective population-based study of embryo transfer cycles in Australia and New Zealand between 2002 and 2006, using data from the Australia and New Zealand Assisted Reproduction Database.

**MAIN OUTCOME MEASURES:** Proportion of SET procedures; comparison of SET and DET procedures with respect to multiple births, low birthweight (LBW), preterm birth and fetal death.

**RESULTS:** The proportion of SET procedures has increased from 28.4% in 2002 to 32.0% in 2003, 40.5% in 2004, 48.2% in 2005 and 56.9% in 2006. The multiple birth rate for all babies conceived by SET (4.0%) was 10 times lower than for those conceived by DET (39.1%) ( $P < 0.01$ ). The average birthweight for all liveborn babies conceived by SET (3290 g) was higher than for those conceived by DET (2934 g) ( $P < 0.01$ ). The preterm birth rate of all DET-conceived babies (30.3%) was higher than for SET-conceived babies (12.3%) (adjusted odds ratio [AOR], 3.19 [95% CI, 3.01-3.38]). All babies conceived by DET were more likely to be stillborn than those conceived by SET (AOR, 1.49 [95% CI, 1.21-1.82]). Singletons conceived by DET were more likely to be born preterm than singletons conceived by SET (AOR, 1.13 [95% CI, 1.05-1.22]). Liveborn singletons conceived by DET were 15% more likely to have LBW than liveborn singletons conceived by SET (AOR, 1.15 [95% CI, 1.05-1.26]). There was no significant difference in fetal death rate between DET- and SET-conceived singletons.

**CONCLUSION:** The increase in proportion of SET procedures has resulted in a lower rate of multiple births and in better perinatal outcomes in Australian and New Zealand assisted reproduction programs.

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Homer C, Clements V, McDonnell N, Peek M, Sullivan E.

**Maternal mortality: What can we learn from stories of postpartum haemorrhage?**

Women Birth. 2009 Mar 9. [Epub ahead of print]

Centre for Midwifery, Child & Family Health, University of Technology Sydney, PO Box 123, Broadway, NSW 2007, Australia.

Death from pregnancy is rare in developed countries such as Australia but is still common in third world and developing countries. The investigation of each maternal death yields valuable information and lessons that all health care providers involved with the care of women can learn from. The aim of these investigations is to prevent future maternal morbidity and mortality. Obstetric haemorrhage remains a leading cause of maternal death internationally. It

is the most common cause of death in developing countries. In Australia and the United Kingdom, obstetric haemorrhage is ranked as the 4th and 3rd most common cause of direct maternal death respectively. In a number of cases there are readily identifiable factors associated with the care that the women received that may have contributed to their death. It is from these identifiable factors that both midwives and doctors can learn to help prevent similar episodes from occurring. This article will identify some of the lessons that can be learnt from the recent Australian and UK maternal death reports. This paper presents an overview of the process and systems for the reporting of maternal death in Australia. It will then specifically focus on obstetric haemorrhage, with a focus on postpartum haemorrhage, for the 12-year period, 1994-2005. Vignettes from the maternal mortality reports in Australia and the United Kingdom are used to highlight the important lessons for providers of maternity care.

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Austin MP, Priest SR, Sullivan EA.

**Antenatal psychosocial assessment for reducing perinatal mental health morbidity.**

Cochrane Database Syst Rev. 2008 Oct 8; (4):CD005124.

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**BACKGROUND:** Mental health conditions arising in the perinatal period, including depression, have the potential to impact negatively on not only the woman but also her partner, infant, and family. The capacity for routine, universal antenatal psychosocial assessment, and thus the potential for reduction of morbidity, is very significant.

**OBJECTIVES:** To evaluate the impact of antenatal psychosocial assessment on perinatal mental health morbidity.

**SEARCH STRATEGY:** We searched the Cochrane Pregnancy and Childbirth Group's Trials Register, the Cochrane Depression, Anxiety and Neurosis Group's Trials Register (CCDAN TR-Studies), HSRProj in the National Library of Medicine (USA), and the Current Controlled Trials website: <http://www.controlledtrials.com/> and the UK National Research Register (last searched March 2008).

**SELECTION CRITERIA:** Randomised and quasi-randomised controlled trials.

**DATA COLLECTION AND ANALYSIS:** At least two review authors independently assessed trials for eligibility; they also extracted data from included trials and assessed the trials for potential bias.

**MAIN RESULTS:** Two trials met criteria for an RCT of antenatal psychosocial assessment. One trial examined the impact of an antenatal tool (ALPHA) on clinician awareness of psychosocial risk, and the capacity of the antenatal ALPHA to predict women with elevated postnatal Edinburgh Depression Scale (EDS) scores, finding a trend towards increased clinician awareness of 'high level' psychosocial risk where the ALPHA intervention had been used (relative risk (RR) 4.61 95% confidence interval (CI) 0.99 to 21.39). No differences between groups were seen for numbers of women with antenatal EDS scores, a score of greater than 9 being identified by ALPHA as of concern for depression (RR 0.69 95% CI 0.35 to 1.38); 139 providers. The other trial reported no differences in EPS scores greater than 12 at 16 weeks postpartum between the intervention (communication about the EDS scores with the woman and her healthcare providers plus a patient information booklet) and the standard care groups (RR 0.86 95% CI 0.61 to 1.21; 371 women).

**AUTHORS' CONCLUSIONS:** While the use of an antenatal psychosocial assessment may increase the clinician's awareness of psychosocial risk, neither of these small studies provides sufficient evidence that routine antenatal psychosocial assessment by itself leads to improved perinatal mental health outcomes. Further studies with better sample size and statistical power are required to further explore this important public health issue. It will also be important to examine outcomes up to one year postpartum not only for mother, but also infant and family.

**Australia: VBDR - HALLIDAY J**

Halliday J, Collins V, Riley M, Youssef D, Muggli E.

**Has prenatal screening influenced the prevalence of comorbidities associated with**

## **Down syndrome and subsequent survival rates?**

Pediatrics. 2009 Jan; 123(1):256-61.

Murdoch Childrens Research Institute, Parkville, Victoria, Australia.

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**OBJECTIVES:** With this study we aimed to compare survival rates for children with Down syndrome in 2 time periods, 1 before prenatal screening (1988-1990) and 1 contemporaneous with screening (1998-2000), and to examine the frequency of comorbidities and their influence on survival rates.

**METHODS:** Record-linkage was performed between the population-based Victorian Birth Defects Register and records of deaths in children up to 15 years of age collected under the auspice of the Consultative Council on Obstetric and Pediatric Mortality and Morbidity. Cases of Down syndrome were coded according to the presence or absence of comorbidities by using the International Classification of Diseases, Ninth Revision classification of birth defects. Kaplan-Meier survival functions and log rank tests for equality of survival distributions were performed.

**RESULTS:** Of infants liveborn with Down syndrome in 1998-2000, 90% survived to 5 years of age, compared with 86% in the earlier cohort. With fetal deaths excluded, the proportion of isolated Down syndrome cases in the earlier cohort was 48.7% compared with 46.1% in the most recent cohort. In 1988-1990 there was at least 1 cardiac defect in 41.1% of cases and in 45.4% in 1998-2000. There was significant variation in survival rates for the different comorbidity groupings in the 1988-1990 cohort, but this was not so evident in the 1998-2000 cohort.

**CONCLUSIONS:** Survival of children with Down syndrome continues to improve, and there is an overall survival figure of 90% to at least 5 years of age. It is clear from this study that prenatal screening technologies are not differentially ascertaining fetuses with Down syndrome and additional defects, because there has been no proportional increase in births of isolated cases with Down syndrome.

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Ponsonby AL, Catto-Smith AG, Pezic A, Dupuis S, Halliday J, Cameron D, Morley R, Carlin J, Dwyer T.

**Association between early-life factors and risk of child-onset Crohn's disease among victorian children born 1983-1998: A birth cohort study.**

Inflamm Bowel Dis. 2008 Dec 23. 15(6):858-866. [Epub ahead of print]

Murdoch Childrens Research Institute, Melbourne, Victoria, Australia.

**BACKGROUND:** The incidence of Crohn's disease (CD) with onset before age 16 has increased. Several perinatal characteristics have been associated with CD. Our objective was to examine the temporal change in CD incidence by period of birth and the extent that this could be attributed to perinatal characteristics associated with higher CD risk.

**METHODS:** A record linkage study was conducted utilizing the perinatal records of Victorian births 1983-1998 inclusive and a state-based CD registry. Proportional hazards models were used to investigate the perinatal factors in relation to the onset of CD by age 16. Further, a nested case control study was conducted to examine the association between sibling exposure and CD risk

**RESULTS:** The CD incidence rate for births 1983-1998 was 2.01 (95% confidence interval [CI] 1.79, 2.27) per 100,000 child-years. A birth cohort effect was demonstrated, with higher CD risk for 1992-1998 versus 1983-1991 births (hazard ratio [HR] 1.56; 95% CI 1.18, 2.06). Perinatal characteristics associated with higher CD risk included urban location, higher socioeconomic status, married mother, a congenital abnormality and delivery by elective cesarean section. Sibling exposure during the first 6 years of life was not associated with CD risk. The increased CD incidence among more recent births was not accounted for by changes in these measured perinatal factors.

**CONCLUSIONS:** The temporal increase in CD incidence documented for births up to 1990 has continued for children born after 1991 and was not accounted for by temporal changes in the measured perinatal factors.

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du Plessis L, Hunt RW, Fletcher AS, Riley MM, Halliday JL.

**What has happened with neural tube defects and womens' understanding of folate in Victoria since 1998?**

Med J Aust. 2008 Nov 17; 189(10):570-4.

Royal Children's Hospital, Melbourne, VIC, Australia.

**OBJECTIVE:** To describe the prevalence of neural tube defects (NTDs) in Victoria, and to evaluate women's knowledge and awareness of the importance of folate after the introduction of voluntary food fortification.

**DESIGN AND SETTING:** Descriptive study, set in Victoria, Australia, based on routinely collected data from the Victorian Birth Defects Register (VBDR) for 1998-2006, and responses by women aged 18-50 years to five questions relating to folate on the 2005 and 2006 Victorian Population Health Surveys (2314 and 2488 women, respectively).

**MAIN OUTCOME MEASURES:** Prevalence of NTDs, and extent of women's knowledge of the importance of folate in NTD prevention, comparing the period before and since voluntary food fortification and a folate awareness campaign.

**RESULTS:** The total prevalence of pregnancies affected by NTDs declined from approximately 17 to 14 per 10,000 births from 1997 to 1999 (coinciding with the period when voluntary food fortification was introduced, and a 1-year folate awareness campaign was held). It has since remained static. Over the 9-year study period, the termination of pregnancy rate was 79%, resulting in three NTD-affected babies per 10,000 livebirths. Compared with women aged 30-34 years (the reference group), those aged 20-24 years had the greatest likelihood of having a baby with an NTD (adjusted odds ratio, 1.70; 95% CI, 1.33-2.18; P < 0.001). Women aged 18-24 years had the lowest rate of folate supplement use (15.9% in 2006), while women aged 30-34 years had the highest rate (30.3% in 2006).

**CONCLUSIONS:** There has been no further reduction in prevalence of NTDs in Victoria since 1999, and this prevalence remains well above that achievable through adequate folate intake. Accurate knowledge of folate consumption, population-based NTD prevalence data and folate awareness data are essential in monitoring the effectiveness of the mandatory fortification program to be implemented in Australia in the next 2 years.

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Gibson K, Halliday JL, Kirby DM, Yaplito-Lee J, Thorburn DR, Boneh A.

**Mitochondrial oxidative phosphorylation disorders presenting in neonates: clinical manifestations and enzymatic and molecular diagnoses.**

Pediatrics. 2008 Nov; 122(5):1003-8.

Metabolic Service, Genetic Health Services Victoria, Victoria and Royal Children's Hospital, Melbourne, Australia.

**OBJECTIVES:** The goals were to examine the frequency of perinatal manifestations of mitochondrial oxidative phosphorylation disorders within a population-based cohort, to characterize these manifestations, to identify a possible association between these manifestations and diagnoses at a later age, and to identify possible associations between perinatal complications and specific disorders.

**METHODS:** We conducted a retrospective review of clinical and laboratory records for all patients with definitive oxidative phosphorylation disorders who were diagnosed and treated at the Royal Children's Hospital in Melbourne between 1975 and 2006 (N = 107; male/female ratio: 1.41).

**RESULTS:** Neonatal presentation was recorded for 32 of 107 patients (male/female ratio: 1:1), including 19 who presented on day 1 of life. Prematurity (gestational age of <37 weeks) was noted for 12.6% of the 107 patients. Of the 85 infants with known birth weights, 24 were in the  $\leq$ 10th percentile for gestational age (11 with complex I deficiency), and 9 of those (6 with complex I deficiency) were in the  $<3^{\text{rd}}$  percentile. The most common presenting neonatal symptoms after the first day of life were poor feeding, recurrent vomiting, and failure to thrive. We noted 3 main clinical neonatal forms of oxidative phosphorylation disorders (encephalomyopathic, hepatointestinal, and cardiac). Of the 32 infants, 28 died (13 in the neonatal period). Complex I deficiency was identified for 15 neonates, combined complexes I, III, and IV deficiency for 7 neonates, and combined complexes I and IV deficiency for 3

neonates. No neonates had complex IV deficiency. Six neonates had nuclear mutations, and 2 neonates had the mitochondrial DNA 8993T>G mutation.

**CONCLUSIONS:** Oxidative phosphorylation disorders present commonly in the neonatal period. The combination of nonspecific manifestations such as prematurity and intrauterine growth retardation with early postnatal decompensation or poor feeding or vomiting and persistent lactic acidosis should suggest the possibility of an oxidative phosphorylation disorder.

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Amor DJ, Halliday J.

**A review of known imprinting syndromes and their association with assisted reproduction technologies.**

Hum Reprod. 2008 Dec; 23(12):2826-34. Epub 2008 Aug 14.

Murdoch Childrens Research Institute, Parkville, Victoria 3052, Australia.

An association between assisted reproduction technologies (ART) and abnormal genomic imprinting in humans has been recognized for several years; however, the magnitude of this risk and the spectrum of imprinting syndromes to which the risk applies remains unknown. Nine human imprinting syndromes have been identified but current evidence links ART with only three: Beckwith-Wiedemann syndrome, Angelman syndrome and the newly described maternal hypomethylation syndrome. There is currently a lack of evidence linking ART with the remaining six imprinting syndromes: Prader-Willi syndrome, Russell-Silver syndrome, maternal and paternal uniparental disomy of chromosome 14, pseudohypoparathyroidism type 1b and transient neonatal diabetes. Evidence from clinical reports suggests that the association between imprinting syndromes and ART may be restricted to syndromes where the imprinting change takes the form of hypomethylation on the maternal allele. In contrast, studies of gametes and early embryos suggest that ART can be associated with hypermethylation as well as hypomethylation, with imprinting changes occurring on paternal as well as maternal alleles. The health effects of ART-associated imprinting changes may also extend beyond the nine recognized imprinting syndromes.

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Herlihy AS, Halliday J.

**Is paternal age playing a role in the changing prevalence of Klinefelter syndrome?**

Eur J Hum Genet. 2008 Oct; 16(10):1173-4; author reply 1174. Epub 2008 May 21.

Comment on: Eur J Hum Genet. 2008 Feb; 16(2):163-70.

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Fernando S, Breheny S, Jaques AM, Halliday JL, Baker G, Healy D.

**Preterm birth, ovarian endometriomata, and assisted reproduction technologies.**

Fertil Steril. 2009 Feb; 91(2):325-30. Epub 2008 Apr 1.

Department of Obstetrics and Gynecology, Monash University, Clayton, Victoria, Australia.

**OBJECTIVE:** To report preterm birth and small for gestational age (SGA) rates from assisted reproduction technologies (ART) patients with ovarian endometriomata compared with control groups.

**DESIGN:** Retrospective cohort study.

**SETTING:** Tertiary university affiliated ART center and Perinatal Data Collection Unit (PDCU).

**PATIENT(S):** Every woman who had an ART singleton baby born between 1991 and 2004 had her database record assessed (N = 4382). Control groups included 1201 singleton babies from ART patients without endometriosis and 2400 randomly selected women from the PDCU database of 850,000 births.

**INTERVENTION(S):** There were 95 singleton ART babies from patients with ovarian endometriomata and 535 ART singleton babies from patients who had endometriosis but no ovarian endometriomata.

**MAIN OUTCOME MEASURE(S):** Preterm birth rates and SGA birth rates.

**RESULT(S):** Preterm birth rate increased only in the ovarian endometriomata group when

compared with community birth records (n = 850,000). Furthermore, ART patients with ovarian endometriomata had a statistically significantly increased likelihood of having a SGA baby when compared with other forms of endometriosis.

**CONCLUSION(S):** Rates of preterm birth and SGA babies doubled in infertility patients with ovarian endometriomata who required ART.

## **Australia WABDR - BOWER C**

Mutch R, Peadon EM, Elliott EJ, **Bower C**.

**Need to establish a national diagnostic capacity for foetal alcohol spectrum disorders.**

J Paediatr Child Health. 2009 Mar; 45(3):79-81.

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Alcohol exposure in pregnancy can induce a broad range of physical and developmental defects in the child, collectively known as foetal alcohol spectrum disorders (FASD). In Australia, there are proven gaps in our knowledge and practice for recognising and diagnosing FASD. The challenge for the Australian health professional is agreeing on a model for diagnosing and treating FASD. The diagnostic method must be evidence based, sensitive and specific, and account for other exposures during pregnancy and early life events. Training in application of the diagnostic method needs to be readily available in metropolitan and regional Australia. The University of Washington FASD 4-digit diagnostic code fulfils all of these best practice criteria, recommending itself as the method of choice.

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Oddy WH, De Klerk NH, Miller M, Payne J, **Bower C**.

**Association of maternal pre-pregnancy weight with birth defects: evidence from a case-control study in Western Australia.**

Aust N Z J Obstet Gynaecol. 2009 Feb; 49(1):11-5.

Telethon Institute of Child Health Research, Centre for Child Health Research, The University of Western Australia, Perth, Western Australia, Australia.

**BACKGROUND:** Maternal obesity confers increased risks of poor pregnancy outcomes. There are limited Australian data on the risk of birth defects associated with maternal pre-pregnancy obesity.

**METHODS:** Population-based case-control study of 418 controls, 111 cases with heart defects (and of these, 38 had conotruncal heart defects), 27 with neural tube defects, 86 cases with urinary tract defects, 48 cases with orofacial clefts, and 20 with limb reduction defects. Maternal pre-pregnancy weight and height were self-reported.

**RESULTS:** Women with pre-pregnancy obesity (body mass index 30+) had a twofold increased odds of having an infant with neural tube defects, conotruncal heart defects, orofacial clefts and limb reduction defects and 30-40% increase in heart defects generally and urinary tract defects. None of the estimates was statistically significant.

**CONCLUSIONS:** Our findings were consistent with similar, statistically significant studies in the literature. Weight reduction prior to pregnancy in obese women may be a means of primary prevention of birth defects.

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Colvin L, Slack-Smith L, Stanley FJ, **Bower C**.

**Pharmacovigilance in pregnancy using population-based linked datasets.**

Pharmacoepidemiol Drug Saf. 2009 Mar; 18(3):211-25.

Centre for Child Health Research, Telethon Institute for Child Health Research, The University of Western Australia, Australia. lync@ichr.uwa.edu.au

**PURPOSE:** National dispensing data for subsidized prescription medicines have recently been approved for linkage to the population-based health datasets in Western Australia (WA), creating the capacity to study how these medicines are used and their impact on pregnancy outcomes.

**METHODS:** Pregnancy events were identified in the Hospital Morbidity Data System from 2002 to 2005 (N = 164,278 admissions; N = 98,265 women) and linked to the midwives' notification system (MNS), the registry of births and deaths, the Western Australian birth defects registry and the pharmaceutical benefit scheme. Dispensing records were extracted for each pregnancy event (N = 1,276,084 dispenses).

**RESULTS:** There were 106,074 births, 1527 ectopic pregnancies and 25,180 terminations of pregnancy. Dispensed medicines were linked to 28.0% of the pregnancy events. Multiple birth pregnancies were 50% more likely to be dispensed a medicine in the first trimester. As parity increased, so did the likelihood of a medicine being dispensed in pregnancy. Women who were dispensed a medicine were twice as likely to smoke during pregnancy and were 14% more likely to have a registered birth defect. During the first trimester, medicines from category D or X of the risk of drug use in pregnancy were dispensed to 2.1% of all pregnancy events. The WHO ATC 'Psychoanaleptics' category was dispensed to 3.8% of all pregnancy events.

**CONCLUSION:** Linkage of dispensing data to pregnancy events is feasible and this approach to post-marketing surveillance will add to the resources available in Australia to investigate pregnancy outcomes in relation to the safe use of prescribed medicines in pregnancy. © 2009 John Wiley & Sons, Ltd.

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O'Leary C, Zubrick SR, Taylor CL, Dixon G, **Bower C**.

**Prenatal alcohol exposure and language delay in 2-year-old children: the importance of dose and timing on risk.**

Pediatrics. 2009 Feb; 123(2):547-54.

Division of Population Sciences, Telethon Institute for Child Health Research, PO Box 855, West Perth, WA 6872, Australia. colleeno@ichr.uwa.edu.au

**OBJECTIVE:** The aim of this study was to investigate the association of dose and timing of prenatal alcohol exposure with early language acquisition.

**METHODS:** We examined language delay in a randomly selected, population-based sample of Western Australian children born in 1995-1996 whose mothers had agreed to participate in a longitudinal study on health-related behaviors and who had completed the 2-year questionnaire (N = 1739). Information on alcohol consumption was collected at 3 months after birth for four periods; the three months pre-pregnancy and for each trimester separately. Prenatal alcohol exposure was grouped into none, low, moderate-heavy and binge (>5) based on the total quantity consumed per week, quantity consumed per occasion, and frequency of consumption. The communication scale from the Ages & Stages Questionnaire was used to evaluate language delay. Logistic regression analysis was used to generate odds ratios and 95% confidence intervals, adjusted for confounding factors.

**RESULTS:** There was no association between low levels of alcohol consumption and language delay at any time period, although there was a nonsignificant 30% increase in risk when moderate-to-heavy levels of alcohol were consumed in the third trimester. Children exposed to a binge pattern of maternal alcohol consumption in the second trimester had nonsignificant, three-fold increased odds of language delay, with a similar estimate following third trimester alcohol exposure after controlling for covariates.

**CONCLUSIONS:** This study did not detect an association between low levels of prenatal alcohol exposure and language delay when compared with women who abstained from alcohol during pregnancy. A nonsignificant threefold increase in the likelihood of language delay was seen in children whose mothers binged during late pregnancy. However, the small numbers of women with a binge-drinking pattern in late pregnancy limited the power of this study; studies analyzing larger numbers of children exposed to binge drinking in late pregnancy are needed.

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Brameld KJ, Dickinson JE, O'Leary P, **Bower C**, Goldblatt J, Hewitt B, Murch A, Stock R.

**First trimester predictors of adverse pregnancy outcomes.**

Aust N Z J Obstet Gynaecol. 2008 Dec; 48(6):529-35.

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AIM: To identify first trimester indicators of adverse pregnancy outcomes.

METHOD: Data were obtained from the statewide evaluation of first trimester screening for Down syndrome in Western Australia which included 22,695 pregnancies screened between August 2001 and October 2003. Screening data were linked with pregnancy outcome information from the Hospital Morbidity Database and the Birth Defects Registry. The odds ratios (OR) of adverse outcomes were analysed for combined risk incorporating maternal age, nuchal translucency (NT) and biochemical parameters and then separately for each parameter (pregnancy-associated plasma protein-A (PAPP-A), free beta human chorionic gonadotropin (beta-hCG) and NT). RESULTS: Risk assessments for first trimester combined screening are derived from maternal age, ultrasound measurement of fetal NT, maternal serum free beta-hCG and PAPP-A. Increased combined risk for Down syndrome was significantly ( $P < 0.01$ ) associated with spontaneous loss at or before 24 weeks gestation (OR 13.51), birth defects (OR 6.58) and preterm birth at or before 32 weeks gestation (OR 3.2). Maternal serum PAPP-A below the 5<sup>th</sup> centile was associated with Down syndrome (OR 8.43), spontaneous loss before 24 weeks (OR 5.04) and later than 24 weeks (OR 4.50), preterm delivery before 32 weeks (OR 3.11) and before 37 weeks (OR 2.24). NT above the 95<sup>th</sup> centile was associated with Down syndrome (OR 43.91), birth defects (OR 4.02) and spontaneous loss before 24 weeks (OR 6.24). Low levels of free beta-hCG and increased NT were less consistently associated with adverse outcomes and high levels of free beta-hCG showed limited use as an indicator. The detection rates for all outcomes other than Down syndrome were less than 40%. CONCLUSION: Biochemical indicators and NT that are measured during first trimester screening for Down syndrome show a number of associations with adverse outcomes, but do not show appropriate performance characteristics for screening tests. These data are consistent with the view that the individual components, specifically low PAPP-A levels alone, do not provide an effective screening tool for adverse pregnancy outcomes.

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Slack-Smith LM, Colvin L, Leonard H, Kilpatrick N, Bower C, Brearley Messer L.

**Factors associated with dental admissions for children aged under five years in Western Australia.**

Arch Dis Child. 2008 Dec 5. [Epub ahead of print]

The University of Western Australia, Australia.

OBJECTIVE: There is limited literature describing dental admissions in preschool children. This paper describes dental hospital admissions and associated factors in children under five years.

DESIGN: This study uses total population data for Western Australia which links midwives' information with birth defects, intellectual disability, hospital admissions and deaths. Children born 1980-1995 ( $n=383,665$ ) were followed until five years. Intellectual disability data were available for children born between 1983 and 1992. Admission data including length of stay were examined.

OUTCOME MEASURES: Admissions for each relevant ICD-9 principal diagnosis category and factors associated with having had a dental admission (all categories) and ICD-9 521 (mostly caries) in particular were investigated.

RESULTS: There were 11,523 dental admissions involving 10,493 children. Of all dental admissions, 76% were in ICD-9 category 521, which included admissions for dental caries. After adjusting for confounders, children with intellectual disability (odds ratio (OR) 1.92; 95% CI 1.63 to 2.27) and birth defect 1.85 (1.68 to 2.05) were more likely to have had a dental admission. Children living in a region without fluoridated water were also more likely to have had a dental admission 2.16 (1.94 to 2.40). Males were more likely to have had a dental admission 1.16 (1.08 to 1.25), as were children with an Indigenous mother 1.17 (1.02 to 1.34). Investigation of ICD-9 521 admissions showed associations similar to those described above except for mother being Indigenous, which was associated with reduced likelihood of admission.

CONCLUSION: Given the burden of dental admissions in young children, these findings highlight

the need for improved oral care for children.

### **Canada-Alberta: ACASS - LOWRY RB**

Lowry RB, Johnson CY, Gagnon F, Little J.

**Segregation analysis of cleft lip with or without cleft palate in the First Nations (Amerindian) people of British Columbia and review of isolated cleft palate etiologies.**

Birth Defects Res A Clin Mol Teratol. 2009 Feb 12. [Epub ahead of print]

Department of Clinical Genetics, Alberta Children's Hospital;  
Alberta Congenital Anomalies Surveillance System, Calgary, Canada.

**BACKGROUND:** The First Nations (Amerindian) population of British Columbia, Canada, has the highest reported birth prevalence in the world of cleft lip with or without cleft palate (CL/P) at nearly 3 per 1000 births. In addition, a substantial proportion of cleft palate only (CPO) cases in this population has been reported to be X-linked. The aims of this study were to perform complex segregation analysis to investigate the mode of inheritance of CL/P in the First Nations people of British Columbia and to review the etiology of the CPO cases.

**METHODS:** All First Nations children born in British Columbia between 1952 and 1971 with an orofacial cleft were included in the study. Multiple sources of ascertainment were used, so that nearly 100% of live births were identified and included during this time. No stillbirths were found but would likely have been ascertained. Extended pedigrees were constructed from these probands and examination of immediate family members, e.g., parents and siblings, was done wherever possible. Complex segregation analysis included all family members. In addition, a CPO case review was conducted.

**RESULTS:** Complex segregation analysis supports the hypothesis that the most likely mode of inheritance of CL/P in this population is a mixed model; that is, an autosomal major gene with polygenic component. The review of 26 CPO cases showed that a substantial proportion are syndromic. Birth Defects Research (Part A), 2009. © 2009 Wiley-Liss, Inc.

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Lowry RB.

**Congenital anomalies surveillance in Canada.**

Can J Public Health. 2008 Nov-Dec; 99(6):483-5.

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Congenital anomalies (CA) are present in approximately 3% of all newborn babies and account for about 12% of paediatric hospital admissions. They represent an important public health problem. Surveillance is especially important so that preventive measures such as folic acid fortification can be properly assessed without resorting to a series of ad hoc studies. Canada's surveillance of CAs is weak, with only Alberta and British Columbia having established systems. Most provinces have perinatal systems but their CA data are incomplete and they do not capture terminations of pregnancy. The same is true of the Public Health Agency of Canada's system. A new system, the Fetal Alert Network, has been proposed for Ontario, which represents a start but will require additional sources of ascertainment if it is to be a truly population-based system for Ontario.

### **China BDSS Beijing - LI Z**

Li Z, Ren A, Liu J, Zhang L, Ye R, Li S, Li Z.

**High prevalence of orofacial clefts in Shanxi Province in northern China, 2003-2004.**

Am J Med Genet A. 2008 Oct 15; 146A(20):2637-43.

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Shanxi Province in northern China has been identified as an area with the highest prevalence of neural tube defects in the world; however, few reports exist on the prevalence of orofacial clefts (OFC). We examined the prevalence of OFC and their association with selected characteristics. Data came from a population-based birth defects surveillance system in four counties of Shanxi Province. The system captures information on all live births, stillbirths of at least 20 weeks gestation, and pregnancy terminations at any gestational age after prenatal diagnosis of a birth defect. Out of 25,355 births in 2003-2004, 83 cases with orofacial clefts were identified resulting in a birth prevalence of 3.27 per 1,000. Other major external birth defects were present in 12 (14.5%) OFC cases. Cleft lip with palate (CLP), cleft lip alone (CL) and cleft palate alone (CP) accounted for 62.0%, 29.6% and 8.4% of OFC cases without additional external defects, respectively. The male to female ratio was 1.04 (95%CI: 0.67-1.60) for all OFC, 1.46 (95%CI: 0.80-2.68) for CLP, 1.23 (95%CI: 0.52-2.91) for CL, 0.46 (95%CI: 0.08-2.51) for CP without additional major external defects, and 0.31(95%CI: 0.08-1.13) for OFC with additional external defects. The prevalence of OFC without additional external defects was increased with decreased maternal age ( $P < 0.05$ ) and increased maternal education ( $P < 0.05$ ). The birth prevalence of OFC in Shanxi Province of northern China is among the highest worldwide. Further studies are required to define the factors associated with excess risk of clefts. 2008 Wiley-Liss, Inc.

### China CBDMN - ZHU J

Bian XM, Liu JT, Qi QW, Jiang YL, Li Y, Liu SY, Hao N, Zhou J, Lü SM, Zhu BS, Wang H, Xu ZF, Pan XY, Liao C, Cai Y, Wang H, Wang Z, Zhu J, Hu YL.

**Second trimester maternal serum screening for Down's syndrome in mainland China: a multi-center prospective study.**

Zhonghua Fu Chan Ke Za Zhi. 2008 Nov; 43(11):805-9.

Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Science, Beijing 100730, China. xmbian@vip.sohu.net

**OBJECTIVE:** To evaluate the performance characteristics of the second trimester double-marker test for the detection of fetal Down's syndrome in mainland China.

**METHODS:** This prospective national multi-centered study used alpha-fetoprotein (AFP) and free beta-subunit of human chorionic gonadotrophin (free beta-hCG) as the serum markers. From May 2004 to September 2006, 11 centers participated in the collection and analysis of maternal serum AFP and free beta-hCG between 14 and 20(+6) weeks of pregnancy. The screening results were calculated using the standard algorithm based on the standard database provided with the analytic software. Patients with an increased risk of Down's syndrome pregnancy ( $>$  or  $= 1/270$ ) were offered genetic amniocentesis. Outcomes of all pregnancies were obtained.

**RESULTS:** A total of 66 132 singleton pregnancies were included in the study. The median maternal age was 27 years. At a cut-off of 1 in 270, the detection rate (DR) based on a Caucasian database was 72% corresponding to a false positive rate (FPR) of 5%, and the DR based on the Chinese database was raised to 76% corresponding to an FPR of 5%.

**CONCLUSION:** The double-marker test using AFP and free beta-hCG is an effective screen strategy for second-trimester detection of fetal Down's syndrome in mainland China. Ethnic variance exists between the Caucasian and Chinese populations. The accuracy of screening is increased by the use of race-specific medians.

### Czech Republic - SIPEK A JR

Gregor V, Sípek A, Calda P, Sípek A Jr, Horáček J, Langhammer P, Petrzílková L, Weisnerová J.

**Ultrasound prenatal diagnostics of birth defects in the Czech Republic in 1994-2007.**

Ceska Gynekol. 2008 Dec; 73(6):340-50.

Oddelení lékařské genetiky, Fakultní Thomayerova nemocnice, Praha.  
vladimir.gregor@ftn.cz

AIM OF STUDY: An analysis of prenatal diagnostics efficiency of selected birth defects in the Czech Republic in 2007. Update of 1994-2007 data according to particular defects.

TYPE OF STUDY: Retrospective epidemiological analysis of pre- and postnatal diagnostics of selected birth defects and prenatal diagnostics efficiency.

MATERIAL AND METHODS: Data on pre- and postnatally diagnosed birth defects in the Czech Republic during 1994-2007 were used. Data on prenatally diagnosed birth defects (and for this terminated pregnancies) were collected from particular departments of prenatal diagnostics, medical genetics and ultrasound diagnostics in the Czech Republic, data on birth defects in births from the National Birth Defects Register (Institute for Health Information and Statistics). Total numbers and mean incidences of selected types of defects (anencephaly, spina bifida, encephalocele, congenital hydrocephalus, omfalocele, gastroschisis, diafragmatic hernia, cystic kidney, renal agenesis/hypoplasia, transposition of great vessels, tetralogy of Fallot, hypoplastic left heart syndrome and coarctation of aorta) during the period under the study were analyzed. Prenatal diagnostics efficiency of these defects was also assessed.

RESULTS: Following total numbers of particular birth defects were registered during the 1994-2007 period: anencephaly 380, spina bifida 559, encephalocele 1134, congenital hydrocephalus 584, omfalocele 351, gastroschisis 389, diafragmatic hernia 325, cystic kidney 698, renal agenesis/hypoplasia 679, transposition of great vessels 797, tetralogy of Fallot 723, hypoplastic left heart syndrome 533 and coarctation of aorta 973. Mean incidences (per 10,000 live births) and prenatal diagnostics rate (% in brackets) were as follows: anencephaly 2.81 (95.65), spina bifida 4.13 (61.12), encephalocele 0.99 (77.04), congenital hydrocephalus 4.32 (49.61), omfalocele 2.59 (54.97), gastroschisis 2.88 (77.30), diafragmatic hernia 2.40 (22.02), cystic kidney 5.16 (24.80), renal agenesis/hypoplasia 5.02 (25.97), transposition of great vessels 6.93 (7.85), tetralogy of Fallot 6.28 (5.87), hypoplastic left heart syndrome 4.63 (39.86) and coarctation of aorta 8.46 (3.80).

CONCLUSIONS: The study gives updated results of ultrasound prenatal diagnostics of selected types of birth defects in the Czech Republic during the 1994-2007 period. Ultrasound prenatal diagnostics contributes to a decrease of some birth defect in a newborn population as well as to changes of their spectrum in births, especially in lethal and most severe ones. Ultrasound prenatal diagnostics experienced both qualitative and quantitative progress in last years in the Czech Republic, resulting in higher efficiency of prenatal detection of major birth defects in population as well as in separating of associated defects and syndromes, particularly those with a general good prognosis.

\* \* \*

Sípek A, Gregor V, Sípek A Jr., Horáček J, Langhammer P, Petržílková L, Wiesnerová J.

**Birth defects in the Czech Republic in 2006.**

Ceska Gynekol. 2008 Dec; 73(6):331-40.

Oddelení lékařské genetiky, Fakultní Thomayerova nemocni, Praha.  
registrvvv@vrozene-vady.cz

AIM OF STUDY: An analysis of occurrence of selected birth defects in the Czech Republic in 2006. Comparison of mean incidences of selected birth defects during the 1994-2006 to previous period data.

TYPE OF STUDY: Retrospective epidemiological analysis of birth defects incidences from the Czech National Birth Defects Register database.

MATERIAL AND METHODS: Data from the National Birth Defects Register (Institute for Health Information and Statistics) in the Czech Republic in the 1994-2006 period were used along with data on prenatally diagnosed and terminated pregnancies from the same period. Mean incidences of selected types of defects (anencephaly, spina bifida, encephalocele, total neural tube defects, congenital hydrocephalus, omfalocele, gastroschisis, total abdominal wall defects, diaphragmatic hernia, renal agenesis/hypoplasia, cystic kidney, Down syndrome and others) in 2006 were analyzed. For a retrospective analysis, already published data on birth defects in the Czech Republic were used.

RESULTS: During 1961-2006 period, totally 6,173,629 children were born on the area of the Czech Republic, out of which almost 105,000 with a birth defect. Mean incidence was 170 per

10,000 live births. In 1994-2006, totally 1,238,398 children were born, out of which more than 42,000 with a birth defect. Mean incidence was 339 per 10,000 live births (with highest value of 414.58 in 2003). In 1994-2006, 6113 cases of prenatally detected birth defects (resulting in pregnancy termination) were registered, in relative numbers 49.3 per 10,000 live births (2006 63.3 per 10,000). During 1961-2006, totally 2028 anencephaly, 2647 spina bifida, 462 encephalocele, 5137 total neural tube defects, 3904 congenital hydrocephalus, 1627 omfalocoele, 941 gastroschisis, 2568 total abdominal wall defects, 1754 cystic kidney, 1475 renal agenesis/hypoplasia, 1442 diaphragmatic hernia, 6328 Down syndrome, 994 oesophageal defects, 1670 anorectal malformations, 6856 cleft lip and/or palate and 4440 cleft palate cases were registered. Current incidences for 2006 and mean incidences for the 1961-2006 period (in brackets), both per 10,000 live births were as follows: anencephaly 2.17 (3.34), spina bifida 4.82 (4.36), encephalocele 1.23 (0.76), total neural tube defects 8.22 (8.47), congenital hydrocephalus 3.78 (6.43), omfalocoele 3.12 (2.68), gastroschisis 2.46 (1.55), total abdominal wall defects 5.57 (4.23), cystic kidney 8.98 (2.89), renal agenesis/hypoplasia 8.60 (2.43), diaphragmatic hernia 3.78 (2.38), Down syndrome 20.32 (10.43), oesophageal defects 1.56 (1.61), anorectal malformations 2.54 (2.71), cleft lip and/or palate 5.47 (11.11) and cleft palate 7.42 (7.19).

**CONCLUSIONS:** The study gives updated results of incidences analysis of both pre- and postnatally diagnosed birth defects in the Czech Republic until 2006. Some birth defect incidences in live birth are decreasing recently (neural tube defects, abdominal wall defects, Down syndrome), some are increasing (oesophageal defects, anorectal malformations). Some incidences in births are influenced by an increased efficiency of diagnostics (renal defects) some remain more or less on the same level (diaphragmatic hernia) or just oscillate (facial defects).

## **England and Wales - RUDDOCK V**

McLaren E, Ruddock V.

**Congenital anomaly notifications 2007, England and Wales.**

Office for National Statistics.

Health Stat Q. 2009 Spring; (41):69-73.

## **France Paris - KHOSHNOOD B**

Khoshnood B, Bouvier-Colle MH, Leridon H, Blondel B.

**Impact of advanced maternal age on fecundity and women's and children's health.**

J Gynecol Obstet Biol Reprod (Paris). 2008 Dec; 37(8):733-47. Epub 2008 Oct 16.

Inserm, UMR S149, IFR69, recherches épidémiologiques sur la santé périnatale et la santé des femmes, 16, avenue Paul-Vaillant-Couturier, 94807 Villejuif cedex, France. babak.khoshnood@inserm.fr

**OBJECTIVE:** There has been a consistent trend towards delayed childbearing in most Western countries. We present a review of the current epidemiological understanding of the effects of advanced maternal age on fecundity, maternal and child health.

**MATERIALS AND METHODS:** A narrative review of the literature based mostly on the key population-based studies on the subject.

**RESULTS:** Delayed

childbearing results in a substantial decrease in fecundity and a considerable increase in fetal loss; risk of the latter is doubled between 20-24 and 40-44 years of age. Other risks include those related to maternal health (maternal mortality and morbidity) and adverse pregnancy outcomes (multiple births, preterm delivery, fetal growth retardation and congenital anomalies).

**CONCLUSION:** Risks

associated with delayed childbearing become significant for maternal age greater than 35 years, and are particularly high for women aged 40 years and greater.

Knowledge about the risks associated with advancing age can be helpful for

couples in their decisions regarding childbearing.

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Slama R, Khoshnood B, Kaminski M.

**How to control for gestational age in studies involving environmental effects on fetal growth.**

Environ Health Perspect. 2008 Jul; 116(7):A284;

### **France: Strasbourg - DORAY B**

Carelle-Calmels N, Saugier-Weber P, Girard-Lemaire F, Rudolf G, Doray B, Guérin E, Kuhn P, Arrivé M, Gilch C, Schmitt E, Fehrenbach S, Schnebelen A, Frébourg T, Flori E.

**Genetic compensation in a human genomic disorder.**

N Engl J Med. 2009 Mar 19; 360(12):1211-6.

Department of Cytogenetics, Strasbourg University Hospital, Strasbourg, France.

Cytogenetic studies of the parents of a girl with the DiGeorge (or velocardiofacial) syndrome, who carried a deletion at 22q11.2, revealed an unexpected rearrangement of both 22q11.2 regions in the unaffected father. He carried a 22q11.2 deletion on one copy of chromosome 22 and a reciprocal 22q11.2 duplication on the other copy of chromosome 22. Genetic compensation, which is consistent with the normal phenotype of the father, was shown through quantitative-expression analyses of genes located within the genetic region associated with the DiGeorge syndrome. This finding has implications for genetic counseling and represents a case of genetic compensation in a human genomic disorder. 2009 Massachusetts Medical Society

\* \* \*

Dolk H, Jentink J, Loane M, Morris J, de Jong-van den Berg LT; EUROCAT Antiepileptic Drug Working Group. Calzolari E, Barisic I, Wellesley D, Garne E, De Vigan C, de Walle H, Bakker M, Gatt M, Melve KK, O'Mahony M, Nelen V, Gillerot Y, Rivieri F, Pierini A, Queisser-Luft A, Poetzsch S, Tucker D, Portillo I, Latos-Bielenska A, Mejnartowicz J, Doray B, Addor MC.

**Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations?**

Neurology. 2008 Sep 2; 71(10):714-22. Epub 2008 Jul 23.

Social Pharmacy, Pharmacoepidemiology and Pharmacotherapy, Groningen University Institute for Drug Exploration (GUIDE), University of Groningen, The Netherlands, Ant. Deusinglaan 1, 9713 AV Groningen The Netherlands. l.t.w.de.jong-van.den.berg@rug.nl

**OBJECTIVE:** To investigate whether first trimester exposure to lamotrigine (LTG) monotherapy is specifically associated with an increased risk of orofacial clefts (OCs) relative to other malformations, in response to a signal regarding increased OC risk.

**METHODS:** Population-based case-control study with malformed controls based on EUROCAT congenital anomaly registers. The study population covered 3.9 million births from 19 registries 1995-2005. Registrations included congenital anomaly among livebirths, stillbirths, and terminations of pregnancy following prenatal diagnosis. Cases were 5,511 nonsyndromic OC registrations, of whom 4,571 were isolated, 1,969 were cleft palate (CP), and 1,532 were isolated CP. Controls were 80,052 nonchromosomal, non-OC registrations. We compared first trimester LTG and antiepileptic drug (AED) use vs nonepileptic non-AED use, for mono and polytherapy, adjusting for maternal age. An additional exploratory analysis compared the observed and expected distribution of malformation types associated with LTG use.

**RESULTS:** There were 72 LTG exposed (40 mono- and 32 polytherapy) registrations. The ORs for LTG monotherapy vs no AED use were 0.67 (95% CI 0.10-2.34) for OC relative to other malformations, 0.80 (95% CI 0.11-2.85) for isolated OC, 0.79 (95% CI 0.03-4.35) for CP, and 1.01 (95% CI 0.03-5.57) for isolated CP. ORs for any AED use vs no AED use were 1.43 (95% CI 1.03-1.93) for OC, 1.21 (95% CI 0.82-1.72) for isolated OC, 2.37 (95% CI 1.54-3.43) for CP, and 1.86 (95% CI 1.07-2.94) for isolated CP. The distribution of other nonchromosomal malformation

types with LTG exposure was similar to non-AED exposed.

**CONCLUSION:** We find no evidence of a specific increased risk of isolated orofacial clefts relative to other malformations due to lamotrigine (LTG) monotherapy. Our study is not designed to assess whether there is a generalized increased risk of malformations with LTG exposure.

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Amor-Guéret M, Dubois-d'Enghien C, Laugé A, Onclercq-Delic R, Barakat A, Chadli E, Bousfiha AA, Benjelloun M, Flori E, **Doray B**, Laugel V, Lourenço MT, Gonçalves R, Sousa S, Couturier J, Stoppa-Lyonnet D.

**Three new BLM gene mutations associated with Bloom syndrome.**

Genet Test. 2008 Jun; 12(2):257-61.

Institut Curie, Centre de Recherche, Orsay, France. mounira.amor@curie.u-psud.fr

Bloom's syndrome (BS) is a rare autosomal recessive disease predisposing patients to all types of cancers affecting the general population. BS cells display a high level of genetic instability, including a 10-fold increase in the rate of sister chromatid exchanges, currently the only objective criterion for BS diagnosis. We have developed a method for screening the BLM gene for mutations based on direct genomic DNA sequencing. A questionnaire based on clinical information, cytogenetic features, and family history was addressed to physicians prescribing BS genetic screening, with the aim of confirming or guiding diagnosis. We report here four BLM gene mutations, three of which have not been described before. Three of the mutations are frameshift mutations, and the fourth is a nonsense mutation. All these mutations introduce a stop codon, and may therefore be considered to have deleterious biological effect. This approach should make it possible to identify new mutations and to correlate them with clinical information.

### **Israel: IBDSP - MERLOB P**

Fischlowitz S, **Merlob P**, Basel-Vanagaite L.

**Isolated familial posterior earlobe indentations**

Am J Med Genet A. 2009 Feb 15; 149A(4):800-1.

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Klinger G, **Merlob P**.

**Selective serotonin reuptake inhibitor induced neonatal abstinence syndrome.**

Isr J Psychiatry Relat Sci. 2008; 45(2):107-13. Review.

Neonatal Intensive Care Unit, Schneider Children's Medical Center of Israel, Petah Tiqva, Israel. gilkl@post.tau.ac.il

Depression is common in women of childbearing age and especially during pregnancy and the postpartum period. Selective serotonin reuptake inhibitors (SSRIs) are increasingly being used to treat depression prior to and throughout pregnancy. Up to 30% of the newborn infants exposed to SSRIs may present with clinical signs during the first days after birth. Neonatal abstinence syndrome (NAS) describes this clinical syndrome resulting from prior prolonged exposure to SSRI induced by cessation of the drug. NAS includes a wide spectrum from mild to severe nonspecific symptoms which were categorized into four groups of effects: central nervous system (depression followed by excitation), gastrointestinal, autonomic and respiratory. A protocol for observation of SSRI-exposed newborns is presented including an objective method (Finnegan score) to monitor onset, progression and improvement of NAS symptoms.

### **Italy: BDRCam - SCARANO G**

Tessa A, Fiermonte G, Dionisi-Vici C, Paradies E, Baumgartner MR, Chien YH, Loguercio C, de

Baulny HO, Nassogne MC, Schiff M, Deodato F, Parenti G, Lane Rutledge S, Antonia Vilaseca M, Melone MA, **Scarano G**, Aldamiz-Echevarría L, Besley G, Walter J, Martinez-Hernandez E, Hernandez JM, Pierri CL, Palmieri F, Santorelli FM.

**Identification of novel mutations in the SLC25A15 gene in hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome: A clinical, molecular, and functional study.**

Hum Mutat. 2009 May; 30(5):741-8.

Molecular Medicine and Metabolism, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Children's Hospital Bambino Gesù, Rome, Italy.

Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome is an autosomal recessive disorder of the urea cycle. With the exception of the French-Canadian founder effect, no common mutation has been detected in other populations. In this study, we collected 16 additional HHH cases and expanded the spectrum of SLC25A15/ORC1 mutations. Eleven novel mutations were identified including six new missense and one microrearrangement. We also measured the transport properties of the recombinant purified proteins in reconstituted liposomes for four new and two previously reported missense mutations and proved that the transport activities of these mutant forms of ORC1 were reduced as compared with the wild-type protein; residual activity ranged between 4% and 19%. Furthermore, we designed three-dimensional (3D)-modeling of mutant ORC1 proteins. While modeling the changes in silico allowed us to obtain new information on the pathomechanisms underlying HHH syndrome, we found no clear-cut genotype-phenotype correlations. Although patient metabolic alterations responded well to low-protein therapy, predictions concerning the long-term evolution of HHH syndrome remain uncertain.

The preference for a hepatic rather than a neurological presentation at onset also continues, largely, to elude us. Neither modifications in oxidative metabolism-related energy, such as those expected in different mtDNA haplogroups, nor sequence variants in SLC25A2/ORC2 seem to be crucial. Other factors, including protein stability and function, and ORC1-ORC2 structural interactions should be further investigated. Hum Mutat 0, 1-8, 2009. © 2009 Wiley-Liss, Inc.

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Garne E, Loane M, Wellesley D, Barisic I, Eurocat Working Group. Collaborators: Salvador J, Latos-Bielenska A, Portillo I, Haeusler M, Addor MC, Bakker MK, **Scarano G**, Wiesel A, Costigan J, O'Mahony MT, Tucker D, de Vigan C, Calzolari E, Doray B, Gatt M, Ariceta G, Gillerot Y.

**Congenital hydronephrosis: prenatal diagnosis and epidemiology in Europe.**

J Pediatr Urol. 2009 Feb; 5(1):47-52. Epub 2008 Nov 5.

Paediatric Department, Kolding Hospital, Kolding, Denmark. egarne@health.sdu.dk

**OBJECTIVE:** To describe prevalence, prenatal diagnosis and epidemiology of congenital hydronephrosis (CH) in Europe.

**MATERIAL AND METHOD:** Data from a large European database for surveillance of congenital malformations (EUROCAT). The 20 participating registries are all based on multiple sources of information and include information about livebirths, fetal deaths with gestational age  $\geq 20$  weeks and terminations of pregnancy after prenatal diagnosis of malformations. Included were all cases with CH and born 1995-2004.

**RESULTS:** There were 3648 cases with CH giving an overall prevalence of 11.5 cases per 10,000 births. The large majority of cases were livebirths (3506, 96% of total) and only 17 cases were fetal deaths and 120 were terminations of pregnancy. Almost all livebirths were alive 1 week after birth. Boys accounted for 72% of all cases. A high proportion of the cases (86%) had an isolated renal malformation. There were large regional differences in prevalence of CH ranging from 2 to 29 per 10,000 births. There was little regional variation in the prevalence of postnatally diagnosed cases while there were large regional differences in prevalence of prenatally diagnosed cases.

**CONCLUSION:** Cases with CH are mainly livebirths, boys and survive the first week after birth. The large difference in prevalence seems to be related to the availability of prenatal screening in the region. The impact of over-diagnosis and potential over-treatment in regions with high prevalence or under-diagnosis with implications for renal function later in life in regions with low prevalence needs further investigation.

## Italy: North East - BIANCA S

Bianca S, Barrano B, Cataliotti A, Indaco L, Ingegnosi C, Ettore G.

**Kabuki syndrome and sex chromosomal anomalies: is it really an association?**  
Fertil Steril. 2009; 91(5):e6. Epub 2009 Mar 17.

Centro di Consulenza Genetica e di Teratologia della Riproduzione, Laboratorio di Citogenetica, Catania, Italy.

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Bianca S, Boemi G, Barrano B, Cataliotti A, Ingegnosi C, Indaco L, Ettore G.

**Mosaic trisomy 20: considerations for genetic counseling.**  
Am J Med Genet A. 2008 Jul 15; 146A(14):1897-8.

## Italy: ISMAC - TENCONI R

Ruggieri M, Iannetti P, Clementi M, Polizzi A, Incorpora G, Spalice A, Pavone P, Praticò AD, Elia M, Gabriele AL, Tenconi R, Pavone L.

**Neurofibromatosis type 1 and infantile spasms.**  
Childs Nerv Syst. 2009 Feb; 25(2):211-6. Epub 2008 Sep 19.

Institute of Neurological Science, National Research Council, Viale R. Margherita, 6, Catania, 95124, Italy. m.ruggieri@isn.cnr.it

**BACKGROUND:** There is no agreement on the prevalence, natural history and outcome of infantile spasms (IS) in neurofibromatosis type 1 (NF1). By contrast, its prevalence and outcome are well characterised in the setting of other neurocutaneous disorders (e.g. tuberous sclerosis).

**MATERIALS AND METHODS:** The aim of the present study was to try to establish a genotype-phenotype correlation in IS in the setting of NF1. A retrospective (years 1990-2000) and prospective (years 2000-2006) study in three paediatric centres in Italy were taken as referral populations for: (1) children with NF1 and (2) neurological problems in childhood.

**RESULTS:** Ten NF1 patients have had IS. The calculated population-based: (1) prevalence of IS in NF1 (0.76%) was higher than the reported frequency of IS in the general population (0.02-0.05%) and (2) frequency of NF1 in the IS series in two out of three centres (0.62-0.90%) was lower than the estimated frequencies in the literature (1.5-3.0%). Patients had psychomotor delay preceding the spasms (50%), symmetrical spasms (50%), typical (80%) and modified (20%) hypsarrhythmia and foci of spikes and waves and a good response to corticosteroid treatment (50%). Outcome was good in 30%. Imaging revealed high-signal foci in atypical locations (sub-cortical and central brain regions). Deoxyribonucleic acid analysis revealed three novel NF1 gene mutations without genotype-phenotype correlation.

**CONCLUSION:** Even though the combination of IS and NF1 does not seem to be coincidental, it is certainly an unusual event in NF1--rarer than in other neurocutaneous disorders. Spasms in NF1 are not associated with specific genetic defects.

## Italy - BIANCHI F

Monti L, Cinquetti R, Guffanti A, Nicassio F, Cremona M, Lavorgna G, Bianchi F, Vignati F, Cittaro D, Taramelli R, Acquati F.

**In silico prediction and experimental validation of natural antisense transcripts in two cancer-associated regions of human chromosome 6.**  
Int J Oncol. 2009 Apr; 34(4):1099-108.

Department of Biotechnology and Molecular Sciences, University of Insubria, I-21100 Varese, Italy.

Antisense transcription has long been recognized as a mechanism involved in the regulation of gene expression. Therefore, several human diseases associated with abnormal patterns of gene expression might display antisense RNA-mediated pathogenetic mechanisms. Such issue could be particularly relevant for cancer pathogenesis, since deregulated gene expression has long been established as a hallmark of cancer cells. Herein, we report on a bioinformatic search for antisense transcription in two cancer-associated regions of human chromosome 6 (6q21 and 6q27). Natural antisense transcripts (NATs) for several genes in both genomic regions were predicted in silico and subsequently validated by strand-specific RT-PCR. Detailed experimental validation by quantitative real-time RT-PCR of five putative cancer related sense-antisense transcript pairs revealed a single candidate tumor suppressor gene (RPS6KA2) whose expression levels display marked cancer-related changes that are likely mediated by its antisense RNA in a breast cancer cell line model.

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**Bianchi F**, Terracini B.

**AIE position paper on waste management and health: work in progress.**

Epidemiol Prev. 2008 Jul-Oct; 32(4-5):181-2.

### **Japan: JAOG - HIRAHARA F**

Hamanoue H, Megarbane A, Tohma T, Nishimura A, Mizuguchi T, Saitsu H, Sakai H, Miura S, Toda T, Miyake N, Niikawa N, Yoshiura K, **Hirahara F**, Matsumoto N.

**A locus for ophthalmo-acromelic syndrome mapped to 10p11.23.**

Am J Med Genet A. 2009 Mar; 149A(3):336-42.

Department of Human Genetics, Yokohama City University Graduate School of Medicine, Yokohama, Japan.

Ophthalmo-acromelic syndrome (OAS, OMIM %206920) is a rare autosomal recessive disease, presenting with clinical anophthalmia and limb anomalies. We recruited three OAS families including a Japanese family with two affected patients and two consanguineous Lebanese families each having an affected. Homozygosity mapping was performed using the 50K SNP chip and additional informative markers. A locus for OAS was mapped to the 422-kb region at 10q11.23, based on the results from the two consanguineous families as well as the consistent data from the Japanese non-consanguineous family. The 422-kb region only contained one gene, MPP7. Although we could not detect any pathological mutations in OAS families analyzed, MPP7 could remain a candidate as aberrant changes might exist beyond our mutation detection methods. Further families are needed to confirm this candidate locus. 2009 Wiley-Liss, Inc.

### **Malta: MCAR - GATT M**

Pedersen RN, Garne E, Loane M, Korsholm L, Husby S; EUROCAT Working Group. Collaborators: Stone D, Nelen V, de Walle H, Haeusler M, Tucker D, **Gatt M**.

**Infantile hypertrophic pyloric stenosis: a comparative study of incidence and other epidemiological characteristics in seven European regions.**

J Matern Fetal Neonatal Med. 2008 Sep; 21(9):599-604.

Department of Paediatrics, Odense University Hospital, Odense, Denmark. rnp@dadlnet.dk

**OBJECTIVE:** The objective of this study was to present epidemiologic data on infantile hypertrophic pyloric stenosis (IHPS) from seven well-defined European regions, and to compare incidence and changes in incidence over time between these regions.

**METHODS:** This was a population-based study using data from registries of congenital malformations (EUROCAT) for a period of more than two decades (1980-2002).

**RESULTS:** A total of 2534 infants were diagnosed with IHPS during the study period, giving an overall incidence of IHPS of 2.0 per 1000 live births (LB), ranging from 0.86 per 1000 LB to 3.96

per 1000 LB in the seven regions. A significant decrease in incidence was observed in two regions and a significant increase in incidence was observed in two other regions. Young maternal age (<20 years) significantly increased the risk of IHPS by 29% (adjusted by region;  $p < 0.01$ ), and at maternal age of 30 years and older the risk decreased significantly ( $p < 0.01$ ).  
**CONCLUSIONS:** There were significant differences in the incidence of IHPS in the seven European populations. No uniform pattern of change in incidence was observed as the populations also differed in relation to trend over time with both significant increases and decreases over time. There is evidence that young maternal age is a risk factor for IHPS.

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Garne E, Loane M, Wellesley D, Barisic I, Eurocat Working Group. Collaborators: Salvador J, Latos-Bielenska A, Portillo I, Haeusler M, Addor MC, Bakker MK, Scarano G, Wiesel A, Costigan J, O'Mahony MT, Tucker D, de Vigan C, Calzolari E, Doray B, **Gatt M**, Ariceta G, Gillerot Y.

**Congenital hydronephrosis: prenatal diagnosis and epidemiology in Europe.**

J Pediatr Urol. 2009 Feb; 5(1):47-52. Epub 2008 Nov 5.

Paediatric Department, Kolding Hospital, Kolding, Denmark. egarne@health.sdu.dk

**OBJECTIVE:** To describe prevalence, prenatal diagnosis and epidemiology of congenital hydronephrosis (CH) in Europe.

**MATERIAL AND METHOD:** Data from a large European database for surveillance of congenital malformations (EUROCAT). The 20 participating registries are all based on multiple sources of information and include information about livebirths, fetal deaths with gestational age  $\geq 20$  weeks and terminations of pregnancy after prenatal diagnosis of malformations. Included were all cases with CH and born 1995-2004.

**RESULTS:** There were 3648 cases with CH giving an overall prevalence of 11.5 cases per 10,000 births. The large majority of cases were livebirths (3506, 96% of total) and only 17 cases were fetal deaths and 120 were terminations of pregnancy. Almost all livebirths were alive 1 week after birth. Boys accounted for 72% of all cases. A high proportion of the cases (86%) had an isolated renal malformation. There were large regional differences in prevalence of CH ranging from 2 to 29 per 10,000 births. There was little regional variation in the prevalence of postnatally diagnosed cases while there were large regional differences in prevalence of prenatally diagnosed cases.

**CONCLUSION:** Cases with CH are mainly livebirths, boys and survive the first week after birth. The large difference in prevalence seems to be related to the availability of prenatal screening in the region. The impact of over-diagnosis and potential over-treatment in regions with high prevalence or under-diagnosis with implications for renal function later in life in regions with low prevalence needs further investigation.

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Dolk H, Jentink J, Loane M, Morris J, de Jong-van den Berg LT; EUROCAT Antiepileptic Drug Working Group. Calzolari E, Barisic I, Wellesley D, Garne E, De Vigan C, de Walle H, Bakker M, **Gatt M**, Melve KK, O'Mahony M, Nelen V, Gillerot Y, Rivieri F, Pierini A, Queisser-Luft A, Poetzsch S, Tucker D, Portillo I, Latos-Bielenska A, Mejnartowicz J, Doray B, Addor MC.

**Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations?**

Neurology. 2008 Sep 2; 71(10):714-22. Epub 2008 Jul 23.

Social Pharmacy, Pharmacoepidemiology and Pharmacotherapy, Groningen University Institute for Drug Exploration (GUIDE), University of Groningen, The Netherlands, Ant. Deusinglaan 1, 9713 AV Groningen The Netherlands. l.t.w.de.jong-van.den.berg@rug.nl

**OBJECTIVE:** To investigate whether first trimester exposure to lamotrigine (LTG) monotherapy is specifically associated with an increased risk of orofacial clefts (OCs) relative to other malformations, in response to a signal regarding increased OC risk.

**METHODS:** Population-based case-control study with malformed controls based on EUROCAT congenital anomaly registers. The study population covered 3.9 million births from 19 registries 1995-2005. Registrations included congenital anomaly among livebirths, stillbirths, and terminations of pregnancy following prenatal diagnosis. Cases were 5,511 nonsyndromic OC

registrations, of whom 4,571 were isolated, 1,969 were cleft palate (CP), and 1,532 were isolated CP. Controls were 80,052 nonchromosomal, non-OC registrations. We compared first trimester LTG and antiepileptic drug (AED) use vs nonepileptic non-AED use, for mono and polytherapy, adjusting for maternal age. An additional exploratory analysis compared the observed and expected distribution of malformation types associated with LTG use.

**RESULTS:** There were 72 LTG exposed (40 mono- and 32 polytherapy) registrations. The ORs for LTG monotherapy vs no AED use were 0.67 (95% CI 0.10-2.34) for OC relative to other malformations, 0.80 (95% CI 0.11-2.85) for isolated OC, 0.79 (95% CI 0.03-4.35) for CP, and 1.01 (95% CI 0.03-5.57) for isolated CP. ORs for any AED use vs no AED use were 1.43 (95% CI 1.03-1.93) for OC, 1.21 (95% CI 0.82-1.72) for isolated OC, 2.37 (95% CI 1.54-3.43) for CP, and 1.86 (95% CI 1.07-2.94) for isolated CP. The distribution of other nonchromosomal malformation types with LTG exposure was similar to non-AED exposed.

**CONCLUSION:** We find no evidence of a specific increased risk of isolated orofacial clefts relative to other malformations due to lamotrigine (LTG) monotherapy. Our study is not designed to assess whether there is a generalized increased risk of malformations with LTG exposure.

### **Northern Netherlands - BAKKER M**

Dolk H, Jentink J, Loane M, Morris J, de Jong-van den Berg LT; EUROCAT Antiepileptic Drug Working Group. Calzolari E, Barisic I, Wellesley D, Garne E, De Vigan C, de Walle H, **Bakker M**, Gatt M, Melve KK, O'Mahony M, Nelen V, Gillerot Y, Rivieri F, Pierini A, Queisser-Luft A, Poetzsch S, Tucker D, Portillo I, Latos-Bielenska A, Mejnartowicz J, Doray B, Addor MC.

**Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations?**

Neurology. 2008 Sep 2; 71(10):714-22. Epub 2008 Jul 23.

Social Pharmacy, Pharmacoepidemiology and Pharmacotherapy, Groningen University Institute for Drug Exploration (GUIDE), University of Groningen, The Netherlands, Ant. Deusinglaan 1, 9713 AV Groningen The Netherlands. l.t.w.de.jong-van.den.berg@rug.nl

**OBJECTIVE:** To investigate whether first trimester exposure to lamotrigine (LTG) monotherapy is specifically associated with an increased risk of orofacial clefts (OCs) relative to other malformations, in response to a signal regarding increased OC risk.

**METHODS:** Population-based case-control study with malformed controls based on EUROCAT congenital anomaly registers. The study population covered 3.9 million births from 19 registries 1995-2005. Registrations included congenital anomaly among livebirths, stillbirths, and terminations of pregnancy following prenatal diagnosis. Cases were 5,511 nonsyndromic OC registrations, of whom 4,571 were isolated, 1,969 were cleft palate (CP), and 1,532 were isolated CP. Controls were 80,052 nonchromosomal, non-OC registrations. We compared first trimester LTG and antiepileptic drug (AED) use vs nonepileptic non-AED use, for mono and polytherapy, adjusting for maternal age. An additional exploratory analysis compared the observed and expected distribution of malformation types associated with LTG use.

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**CONCLUSION:** We find no evidence of a specific increased risk of isolated orofacial clefts relative to other malformations due to lamotrigine (LTG) monotherapy. Our study is not designed to assess whether there is a generalized increased risk of malformations with LTG exposure.

### **Norway: MBRN - VOLLSET SE**

Boyles AL, Wilcox AJ, Taylor JA, Shi M, Weinberg CR, Meyer K, Fredriksen A, Ueland PM, Johansen

AM, Drevon CA, Jugessur A, Trung TN, Gjessing HK, Vollset SE, Murray JC, Christensen K, Lie RT. **Oral facial clefts and gene polymorphisms in metabolism of folate/one-carbon and vitamin A: a pathway-wide association study.** Genet Epidemiol. 2009 Apr; 33(3):247-55.

Epidemiology Branch, NIEHS/NIH, Durham, North Carolina 27709, USA. boylesa@niehs.nih.gov

An increased risk of facial clefts has been observed among mothers with lower intake of folic acid or vitamin A around conception. We hypothesized that the risk of clefts may be further moderated by genes involved in metabolizing folate or vitamin A. We included 425 case-parent triads in which the child had either cleft lip with or without cleft palate (CL/P) or cleft palate only (CPO), and no other major defects. We analyzed 108 SNPs and one insertion in 29 genes involved in folate/one-carbon metabolism and 68 SNPs from 16 genes involved in vitamin A metabolism. Using the Triad Multi-Marker (TRIMM) approach we performed SNP, gene, chromosomal region, and pathway-wide association tests of child or maternal genetic effects for both CL/P and CPO. We stratified these analyses on maternal intake of folic acid or vitamin A during the periconceptional period. As expected with this high number of statistical tests, there were many associations with P-values < 0.05; although there were fewer than predicted by chance alone. The strongest association in our data (between fetal FOLH1 and CPO, P=0.0008) is not in agreement with epidemiologic evidence that folic acid reduces the risk of CL/P in these data, not CPO. Despite strong evidence for genetic causes of oral facial clefts and the protective effects of maternal vitamins, we found no convincing indication that polymorphisms in these vitamin metabolism genes play an etiologic role.

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Shaw GM, Carmichael SL, Vollset SE, Yang W, Finnell RH, Blom H, Middtun Ø, Ueland PM. **Mid-pregnancy cotinine and risks of orofacial clefts and neural tube defects.** J Pediatr. 2009 Jan; 154(1):17-9. Epub 2008 Nov 5.

March of Dimes California Research Division, Children's Hospital Oakland Research Institute, Oakland, CA 94609, USA. gshaw@marchofdimes.com

**OBJECTIVE:** Past studies of cigarette smoking as a contributor to orofacial clefts and neural tube defects (NTDs) used self-reports of smoke exposures. We have correlated measurements of cotinine (a nicotine metabolite) in mid-pregnancy sera with clefts and NTDs.

**STUDY DESIGN:** From a repository of >180 000 mid-pregnancy serum specimens collected in California from 2003 to 2005 and linked to delivery outcome information, we identified 89 orofacial cleft-associated pregnancies, 80 NTD-affected pregnancies, and randomly selected 409 pregnancy specimens that corresponded to infants without malformations as control subjects. Cotinine was measured by liquid chromatography-mass spectrometry. No smoke exposure was defined as cotinine values < 2 ng/mL, and any exposure was defined as ≥ 2 ng/mL.

**RESULTS:** We observed odds ratios of 2.1 (95% CI, 1.0-4.4) for clefts and 0.4 (95% CI, 0.1-1.7) for NTDs associated with exposure. After adjusting for race/ethnicity, age, and serum folate levels, odds ratios were 2.4 (95% CI, 1.1-5.3) and 0.6 (95% CI, 0.1-2.5). We explored 2 cotinine levels, 2 to 10 ng/mL and >10 ng/mL for clefts (data were too sparse for NTDs). Odds ratios for these levels were 3.3 (95% CI, 0.9-11.9) and 1.7 (95% CI, 0.7-4.2), respectively.

**CONCLUSION:** Smoking exposures, as measured with cotinine levels during mid-pregnancy, were associated with increased risks of clefts and possibly reduced risks of NTDs.

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Engesaeter IØ, Lie SA, Lehmann TG, Furnes O, Vollset SE, Engesaeter LB. **Neonatal hip instability and risk of total hip replacement in young adulthood: follow-up of 2,218,596 newborns from the Medical Birth Registry of Norway in the Norwegian Arthroplasty Register.** Acta Orthop. 2008 Jun; 79(3):321-6.

The Norwegian Arthroplasty Register, Department of Orthopaedic Surgery, Haukeland

University Hospital, Unifob, Bergen. ingvild.engesater@student.uib.no

**BACKGROUND AND PURPOSE:** Dysplasia is probably the most common underlying condition in osteoarthritis of the hip, leading to total hip replacement (THR) in young adulthood. We investigated whether hip instability at birth predisposes to THR in young adulthood.

**METHODS:** Since 1967, all newborns in Norway have been screened for neonatal hip instability (NHI) and the results have been reported to the Medical Birth Registry of Norway (MBRN). In the period 1967-2004, 2,218,596 newborns were registered. From 1987 to 2004, 442 of these individuals had been reported to the Norwegian Arthroplasty Register (NAR) after undergoing total hip replacement (mean age 25 (12-36) years).

**RESULTS:** Neonatal hip instability was reported in 19,432 newborns (0.88%) in the MBRN; according to the NAR, they had a 2.6 (CI 1.4-4.8) times increased risk of THR in young adulthood compared to those without NHI. The absolute risk was low, however; only 57 (95% CI: 30-105) in 10(5) for patients with NHI compared to 20 (95% CI: 18-22) in 10(5) for those without registered hip pathology. Of the 442 patients with THR, 95 were operated because of osteoarthritis of the hip secondary to dysplasia, according to the surgeon's report. However, only 8 of these 95 patients had been reported to have hip instability at birth.

**INTERPRETATION:** Neonatal hip instability increases the risk of THR in young adulthood. Unexpectedly, only 8% of those who underwent THR due to dysplasia were reported to have unstable hips at birth. Our results indicate that clinical testing for NHI is insufficient as a screening method for dysplastic hips that require THR in young adulthood.

### **South Africa SABDSS - BOURNE D †**

**Bourne DE**, Thompson M, Brody LL, Cotton M, Draper B, Laubscher R, Abdullah MF, Myers JE.

**Emergence of a peak in early infant mortality due to HIV/AIDS in South Africa.**

AIDS. 2009 Jan 2; 23(1):101-6.

School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa.  
David.Bourne@uct.ac.za

**OBJECTIVES:** South Africa has among the highest levels of HIV prevalence in the world. Our objectives are to describe the distribution of South African infant and child mortality by age at fine resolution, to identify any trends over recent time and to examine these trends for HIV-associated and non HIV-associated causes of mortality.

**METHODS:** A retrospective review of vital registration data was conducted. All registered postneonatal deaths under 1 year of age in South Africa for the period 1997-2002 were analysed by age in months using a generalized linear model with a log link and Poisson family.

**RESULTS:** Postneonatal mortality increased each year over the period 1997-2002. A peak in HIV-related deaths was observed, centred at 2-3 months of age, rising monotonically over time.

**CONCLUSION:** We interpret the peak in mortality at 2-3 months as an indicator for paediatric AIDS in a South African population with high HIV prevalence and where other causes of death are not sufficiently high to mask HIV effects. Intrauterine and intrapartum infection may contribute to this peak. It is potentially a useful surveillance tool, not requiring an exact cause of death. The findings also illustrate the need for early treatment of mother and child in settings with very high HIV prevalence.

### **South America ECLAMC - CASTILLA EE**

Wehby GL, Murray JC, **Castilla EE**, Lopez-Camelo JS, Ohsfeldt RL.

**Prenatal care effectiveness and utilization in Brazil.**

Health Policy Plan. 2009; 2009 May; 24(3):175-88. Epub 2009 Mar 12.

MPH, PhD, Assistant Professor, Dept of Health Management and Policy, College of Public Health, University of Iowa, Iowa City, IA, USA.

The impact of prenatal care use on birth outcomes has been understudied in South American countries. This study assessed the effects of various measures of

prenatal care use on birth weight (BW) and gestational age outcomes using samples of infants born without and with common birth defects from Brazil, and evaluated the demand for prenatal care. Prenatal visits improved BW in the group without birth defects through increasing both fetal growth rate and gestational age, but prenatal care visits had an insignificant effect on BW in the group with birth defects when adjusting for gestational age. Prenatal care delay had no effects on BW in both infant groups but increased preterm birth risk in the group without birth defects. Inadequate care versus intermediate care also increased LBW risk in the group without birth effects. Quantile regression analyses revealed that prenatal care visits had larger effects at low compared with high BW quantiles. Several other prenatal factors and covariates such as multivitamin use and number of previous live births had significant effects on the studied outcomes. The number of prenatal care visits was significantly affected by several maternal health and fertility indicators. Significant geographic differences in utilization were observed as well. The study suggests that more frequent use of prenatal care can increase BW significantly in Brazil, especially among pregnancies that are uncomplicated with birth defects but that are at high risk for low birth weight. Further research is needed to understand the effects of prenatal care use for pregnancies that are complicated with birth defects.

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**Castilla EE, Orioli IM.**

**Letter to the editor. Liu Q, Yang M L, Li Z J, Bai X F, Wang XK, Lu L, Wang Y X. A simple and precise classification for cleft lip and palate: a five digit numerical recording system.**

Cleft Palate Craniofac J. 2007; 44:465-8.

Cleft Palate Craniofac J. 2009 Mar; 46(2):220. Epub 2008 Jun 28.

\* \* \*

Wehby GL, Murray JC, **Castilla EE**, Lopez-Camelo JS, Ohsfeldt RL.

**Prenatal care demand and its effects on birth outcomes by birth defect status in Argentina.**

Econ Hum Biol. 2009 Mar; 7(1):84-95. Epub 2008 Oct 30.

Department of Health Management and Policy, College of Public Health, University of Iowa, E204, GH, Iowa City, IA 52242, USA. george-wehby@uiowa.edu

Our objective was to identify determinants of prenatal care demand and evaluate the effects of this demand on low birth weight and preterm birth. Delay in initiating prenatal care was modeled as a function of pregnancy risk indicators, enabling factors, and regional characteristics. Conditional maximum likelihood (CML) estimation was used to model self-selection into prenatal care use when estimating its effectiveness. Birth registry data was collected post delivery on infants with and without common birth defects born in 1995-2002 in Argentina using a standard procedure. Several maternal health and fertility indicators had significant effects on prenatal care use. In the group without birth defects, prenatal care delay increased significantly LBW and preterm birth when accounting for self-selection using the CML model but not in the standard probit model. Prenatal care was found to be ineffective on average in the birth defect group. The self-selection of higher risk women into earlier initiation of prenatal care resulted in underestimation of prenatal care effectiveness when using a standard probit model with several covariates. Large improvements in birth outcomes are suggested with earlier initiation of prenatal care for pregnancies uncomplicated with birth defects in Argentina, implying large opportunity costs from the long waiting time observed in this sample (about 17 weeks on average). The suggested ineffectiveness for pregnancies complicated with common birth defects deserves further research.

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Wehby GL, Murray JC, **Castilla EE**, Lopez-Camelo JS, Ohsfeldt RL.

**Quantile effects of prenatal care utilization on birth weight in Argentina.**

Health Econ. 2009 Jan 13. [Epub ahead of print]

Department of Health Management and Policy, College of Public Health, University of Iowa, Iowa City, IA, USA.

The effects of prenatal care utilization on birth weight (BW) may vary by unobserved fetal health endowments. This heterogeneity will be masked by estimating the effects at BW mean but can be evaluated by estimating the effects at BW quantiles as fetal health endowment is a strong correlate with the BW quantile order. We estimated the effects of prenatal care visits and delay before prenatal care initiation, on BW mean and quantiles using a sample of infants from Argentina. Self-selection into prenatal care was modeled using 2SLS and instrumental variable quantile regression. Results suggest that the 'mean' effect of prenatal care utilization largely underestimates the effects at lower BW quantiles. About 35 and 77 g increase in BW mean and 0.1 quantile respectively, per visit and about 30 and 139 g decrease in BW mean and 0.1 quantile respectively, per week delayed, were estimated. Ignoring self-selection into prenatal care resulted in underestimation of mean and quantile effects. Results highlight the limitation of analyses focused on 'mean effects' in the presence of treatment heterogeneity and emphasize the importance of identifying women at risk for having infants at lower BW quantiles as they may benefit most from earlier and more intensive prenatal care. Copyright © 2008 John Wiley & Sons, Ltd.

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Wehby GL, Castilla EE, Lopez-Camelo JS, Murray JC.

**Predictors of multivitamin use during pregnancy in Brazil.**

Int J Public Health. 2009; 54(2):78-87.

College of Public Health, Department of Health Management and Policy, University of Iowa, E204, GH, Iowa City, IA 52242, USA. george-wehby@uiowa.edu

**OBJECTIVES:** The study aimed at identifying predictors of multivitamin use during pregnancy in Brazil.

**METHODS:** Birth registry data of 1,774 infants at maternity hospitals in Brazil were used. The effects of maternal health and fertility risk indicators, enabling factors and other maternal characteristics on multivitamin use were evaluated both pooled and stratified by African ancestry.

**RESULTS:** About 14% of the women used multivitamins during pregnancy. Number of previous live births, maternal age and education, number of ultrasound exams and year of pregnancy had significant effects on multivitamin use in the group reporting African ancestry. Maternal acute illnesses and education had significant effects on use in the group without African ancestry. Significant geographic variation in multivitamin use was observed in both groups.

**CONCLUSIONS:** The study identifies several risk indicators, health care access and enabling factors that are predictive of multivitamin use with differences by African ancestry. The study highlights the importance of increasing the awareness of women of childbearing age of the benefits of multivitamin use and identifies barriers that need to be addressed to promote use.

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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 Oct; 98(10):1833-40. Epub 2008 Feb 28.

Tobacco Control Research Branch, National Cancer Institute, Executive Plaza North, Room 4038, 6130 Executive Blvd, MSC 7337, Bethesda, MD 20892-7337, USA. blochm@mail.nih.gov

**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.

## **Spain: ECEMC - MARTINEZ-FRIAS ML**

Rodríguez L, Martínez-Fernández ML, Aceña MI, López Mendoza S, Martín Fumero L, Rodríguez de Alba M, Gallego-Merlo J, **Martínez-Frías ML**.

**Dicentric inverted duplication of entire 4p arm with no apparent deletion and internal placing of the (-TTAGGG-)n sequence: Description of the first patient.**

Am J Med Genet A. 2009 May; 149A(5):1058-61.

Estudio Colaborativo Español de Malformaciones Congénitas (ECEMC) del Centro de Investigación sobre Anomalías Congénitas (CIAC), Instituto de Salud Carlos III, Madrid, Spain.

\* \* \*

**Martínez-Frías ML**, Bermejo E, Mendioroz J, Rodríguez-Pinilla E, Blanco M, Egüés J, Félix V, García A, Huertas H, Nieto C, López JA, López S, Paísá L, Rosa A, Vázquez MS.

**Epidemiological and clinical analysis of a consecutive series of conjoined twins in Spain.**

J Pediatr Surg. 2009 Apr; 44(4):811-20.

ECEMC, Centro de Investigación sobre Anomalías Congénitas, del Instituto de Salud Carlos III, Madrid, Spain. [mlmartinez.frias@isciii.es](mailto:mlmartinez.frias@isciii.es)

**PURPOSE:** The aim of the study was to analyze the frequency and certain epidemiological characteristics of a consecutive series of conjoined twins born in Spain.

**MATERIAL AND METHODS:** We used data from the Spanish Collaborative Study of Congenital Malformations for the period April 1976 to 2006. Because the Spanish law permitting voluntary termination of pregnancies (TOP) when the fetus presented malformations was effective by the end of 1985, we analyzed the data in 4 periods, 2 before 1986 and 2 after. During the first period (1976-1979) only live births were recorded, whereas both still and live births were included in the other three (1980-1985, 1986-1995, and 1996-2006). In the present study, the cases were classified as symmetrical (16 pairs) and asymmetrical (1 pair) conjoined twins. Each pair of conjoined twins was considered as only one case for calculations, regardless of the type of union.

**RESULTS:** Among a total of 2,281,604 consecutive births between 1980 and 2006, there were a total of 15 cases of symmetrical conjoined twins giving a frequency of 0.70 per 100,000 (1/152,107), whereas there was only 1 stillborn asymmetrical conjoined twin pair (0.04/100,000). Among the 13,418 consecutive stillborns surveyed, 6 cases of conjoined twins were identified (either symmetrical or asymmetrical) giving a frequency of 44.72 per 100,000, and 11 pairs were identified among the 2,425,583 total live births surveyed during the first period 1976 to 1979, a frequency of 0.45 per 100,000. Thus, the frequency among stillborn infants is 99.34 times higher than that observed among live births. However, the frequency for the total births (3 last periods) showed a decreasing trend from 1.47 per 100,000 birth in the first period (1980-1985) when TOP was illegal, to a value of 0.09 per 100,000 in the last period, more than 16-fold lower, probably because of the TOP of affected fetuses. Therefore, we consider that the frequencies observed in the period 1980 to 1985 are the basal values in our population. The most frequent type observed was thoracopagus, with an overall prevalence at birth of 0.44 per 100,000 (1/228,160) from 1980 to 2006, representing 58.82% of the total

population of symmetric conjoined twin pairs. Diprosopus pairs were the next most common group (11.76%). Most of the cases were females (4 males/11 females), and although this appeared to be mainly because of the thoracopagus pairs (males-females, 2:8), in such a small number of cases, it is not possible to determine the ratios for the other groups. Gestational age was significantly shorter than in control twins for each type studied.

**CONCLUSIONS:** We conclude that it is incorrect to consider that all types of conjoined twins have the same epidemiological characteristics, such as the frequency at birth. The differences observed may be related with the distinct embryo-fetal mortality of each type of conjoined twins in different populations, and the sex ratio, among others.

\* \* \*

**Martínez-Frías ML**; ECEMC Working Group. Collaborators: Bermejo E, Mendioroz J, Cuevas L, Félix V, Nieto C, Beseler B, Sanchis A, Zuazo E.

**Epidemiology of acephalus/acardius monozygotic twins: new insights into an epigenetic causal hypothesis.**

Am J Med Genet A. 2009 Feb 15; 149A(4):640-9.

ECEMC, Centro de Investigación sobre Anomalías Congénitas, Instituto de Salud Carlos III, Madrid, Spain. mlmartinez.frias@isciii.es

Apart from a series of 10 acephalus/acardius (Ac/Ac) cases described from a pathological point of view, and the analysis of a review of published cases, we have been unable to find any epidemiological studies on Ac/Ac. Using data from the Spanish Collaborative Study of Congenital Malformations (ECEMC), we present here what seems to be the first epidemiological analysis of a consecutive series of the Ac/Ac type of monozygotic twins (MZT). Among a total of 2,281,604 consecutive births, 11 cases of Ac/Ac MZT were detected, giving a frequency of 0.48 per 100,000 births. However, we consider the period 1980-1985 as the baseline for our data, as in this period voluntary termination of pregnancy was not possible in Spain, and the frequency of Ac/Ac MZT was 0.49 per 100,000 births. Nonetheless, this frequency should be considered as a minimal estimation. The characteristics of these Ac/Ac cases indicate that they are more frequent in males (sex ratio 2.67). In addition, gestational age in Ac/Ac cases was 2.41 and 3.12 weeks lower than in malformed and control twins, respectively. Similarly, their mothers are 4.54 and 4.68 years younger than mothers of separate malformed and control twins, respectively. To understand the biological basis behind the occurrence of MZT in the context of recent observations, we evaluate the hypothesis that the epigenetic processes involved in the early cleavage of the embryo, and in blastocyst formation during development, may be implicated in twinning.

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Bonaglia MC, Ciccone R, Gimelli G, Gimelli S, Marelli S, Verheij J, Giorda R, Grasso R, Borgatti R, Pagone F, Rodríguez L, **Martínez-Frías ML**, van Ravenswaaij C, Zuffardi O.

**Detailed phenotype-genotype study in five patients with chromosome 6q16 deletion: narrowing the critical region for Prader-Willi-like phenotype.**

Eur J Hum Genet. 2008 Dec; 16(12):1443-9. Epub 2008 Jul 23.

Scientific Institute E Medea, Bosisio Parini, Lecco, Italy. clara.bonaglia@bp.lnf.it

Most patients with an interstitial deletion of 6q16 have Prader-Willi-like phenotype, featuring obesity, hypotonia, short hands and feet, and developmental delay. In all reported studies, the chromosome rearrangement was detected by karyotype analysis, which provides an overview of the entire genome but has limited resolution. Here we describe a detailed clinical presentation of five patients, two of whom were previously reported, with overlapping interstitial 6q16 deletions and Prader-Willi-like phenotype. Our patients share the following main features with previously reported cases: global developmental delay, hypotonia, obesity, hyperphagia, and eye/vision anomalies. All rearrangement breakpoints have been accurately defined through array-CGH at about 100 Kb resolution. We were able to narrow the shortest region of deletion overlap for the presumed gene(s) involved in the Prader-Willi-like syndrome to 4.1 Mb located at 6q16.1q16.2. Our results support the evidence that haploinsufficiency of the SIM1 gene is responsible for obesity in these patients. A possible involvement of the GRIK2

gene in autistic-like behaviour, of POPDC3 in heart development, and of MCHR2 in the control of feeding behaviour and energy metabolism is also hypothesized.

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Mendioroz J, Bermejo E, Marshall JD, Naggert JK, Collin GB, **Martínez-Frías ML**.

**Alström syndrome: clinical and genetic features, and a diagnostic guide to foresee complications**

Med Clin (Barc). 2008 Nov 29; 131(19):741-6.

ECEMC, Centro de Investigación sobre Anomalías Congénitas (CIAC), Instituto de Salud Carlos III, Madrid, Spain.

**BACKGROUND AND OBJECTIVE:** Alström syndrome is a progressive autosomal recessive genetic disorder affecting multiple organ systems. It may be detected at birth or in early childhood. Clinically, patients with Alström syndrome develop cone-rod dystrophy leading to eventual blindness, sensorineural deafness, and normal intelligence. Patients develop obesity, endocrine disturbances such as type 2 diabetes mellitus, dilated cardiomyopathy and progressive renal and hepatic failure. Alström syndrome is caused by specific mutations in the ALMS1 gene, located at chromosome 2p13.

**PATIENTS AND METHOD:** A case of a 23 year old patient with Alström syndrome, with a previous diagnosis of Laurence-Moon-Bardet-Biedl is described.

**RESULTS:** The subsequent molecular study revealed a mutation on the ALMS1 gene, confirming the diagnosis of Alström syndrome.

**CONCLUSIONS:** The low frequency, the progressive multi-systemic disturbances, and the similarities with other well-known syndromes may difficult the diagnosis of Alström syndrome. Thus, without a careful examination, it may be misdiagnosed and it would not be possible to perform any anticipatory therapeutic approach, with dramatic consequences for the patients and their families. Moreover, as these patients must have a multidisciplinary approach, they may not receive the adequate treatment on time. therefore, it seems important to publish this case in our country, among with the clinical and molecular characteristics of this syndrome, and to spread a diagnostic and anticipatory guidance for its early detection.

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Rodríguez L, Diego-Alvarez D, Lorda-Sanchez I, Gallardo FL, Martínez-Fernández ML, Arroyo-Muñoz ME, **Martínez-Frías ML**.

**A small and active ring X chromosome in a female with features of Kabuki syndrome.**

Am J Med Genet A. 2008 Nov 1; 146A(21):2816-21.

Estudio Colaborativo Español de Malformaciones Congénitas, Centro de Investigación sobre Anomalías Congénitas, Instituto de Salud Carlos III, Ministerio de Sanidad y Consumo, Madrid, Spain. laura@isciii.es

A ring X chromosome is found in about 6% of patients with Turner syndrome (TS), often with mosaicism for a 45,X cell line. Patients with this karyotype are reported to have a higher incidence of a more severe phenotype including mental retardation. In fact, some studies have shown a correlation between this severity and the presence or absence of an intact and functional X inactivation center (XIST). However, the phenotype of the individuals with r(X) cannot be entirely defined in terms of their X-inactivation patterns. Nevertheless, a small group of these patients have been described to manifest clinical features reminiscent of the Kabuki syndrome. Here we present a female patient with clinical features resembling Kabuki syndrome and a mos 45,X/46,X,r(X) karyotype. Methylation analyses of polymorphic alleles of the androgen receptor gene showed that both alleles were unmethylated suggesting an active ring chromosome. A specific X chromosome array CGH was performed estimating the size of the ring to be 17 Mb, lacking the XIST gene, and including some genes with possible implications in the phenotype of the patient. Copyright 2008 Wiley-Liss, Inc.

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Sanchis Calvo A, Cerveró Martí L, **Martínez Frías ML**.

**Aicardi-Goutières syndrome. Review of the genetic bases and their mechanisms.**  
An Pediatr (Barc). 2008 Nov; 69(5):496-7.

### **Sweden - ANNEREN G**

Nyström AM, Ekvall S, Strömberg B, Holmström G, Thuresson AC, **Annerén G**, Bondeson ML.  
**A severe form of Noonan syndrome and autosomal dominant café-au-lait spots -evidence for different genetic origins.**  
Acta Paediatr. 2009 Apr; 98(4):693-8. Epub 2008 Dec 18.

Department of Genetics and Pathology, Uppsala University, Uppsala, Sweden.

**AIM:** The clinical overlap among Noonan syndrome (NS), cardio-facio-cutaneous (CFC), LEOPARD and Costello syndromes as well as Neurofibromatosis type 1 is extensive, which complicates the process of diagnosis. Further genotype-phenotype correlations are required to facilitate future diagnosis of these patients. Therefore, investigations of the genetic cause of a severe phenotype in a patient with NS and the presence of multiple café-au-lait spots (CAL) spots in the patient and four members of the family were performed.

**METHODS:** Mutation analyses of candidate genes, PTPN11, NF1, SPRED1 and SPRED2, associated with these syndromes, were conducted using DNA sequencing.

**RESULTS:** A previously identified de novo mutation, PTPN11 F285L and an inherited NF1 R1809C substitution in the index patient were found. However, neither PTPN11 F285L, NF1 R1809C, SPRED1 nor SPRED2 segregated with CAL spots in the family. The results indicate that the familial CAL spots trait in this family is caused by a mutation in another gene, distinct from previous genes associated with CAL spots in these syndromes.

**CONCLUSION:** We suggest that the atypical severe symptoms in the index patient may be caused by an additive effect on the F285L mutation in PTPN11 by another mutation, for example the NF1 R1809C or alternatively, the not yet identified gene mutation associated with CAL spots in this family.

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Wentzel C, Fernström M, Ohrner Y, **Annerén G**, Thuresson AC.  
**Clinical variability of the 22q11.2 duplication syndrome.**  
Eur J Med Genet. 2008 Nov-Dec; 51(6):501-10. Epub 2008 Jul 29.

Department of Genetics and Pathology, Uppsala University, Uppsala, Sweden.

The 22q11.2 duplication syndrome is an extremely variable disorder with a phenotype ranging from normal to learning disability and congenital defects. Both patients with a de novo 22q11.2 duplication and patients in whom the duplication has been inherited from a phenotypically normal parent have been reported. In this study we present two familial cases with a 3Mb 22q11.2 duplication detected by array-CGH. We also review the findings in 36 reported cases with the aim of delineating the phenotype of the 22q11.2 duplication syndrome. In a majority of the reported cases where parents have been tested, the duplication seems to have been inherited from a normal parent with minor abnormalities. With this in mind we recommend that family members of patients with a 22q11.2 duplication to be tested for this genetic defect.

### **USA-Atlanta: MACDP- CORREA A**

Ramadhani T, Short V, Canfield MA, Waller DK, **Correa A**, Royle M, Scheuerle A; National Birth Defects Prevention Study (NBDPS).

**Are birth defects among Hispanics related to maternal nativity or number of years lived in the United States?**

Birth Defects Res A Clin Mol Teratol. 2009 Apr 6. [Epub ahead of print]

Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health

Services, Austin, Texas.

**BACKGROUND:** Literature on the risk of birth defects among foreign- versus U.S.-born Hispanics is limited or inconsistent. We examined the association between country of birth, immigration patterns, and birth defects among Hispanic mothers.

**METHODS:** We used data from the National Birth Defects Prevention Study and calculated odds ratios (ORs) and 95% confidence intervals and assessed the relationship between mothers' country of birth, years lived in the United States, and birth defects among 575 foreign-born compared to 539 U.S.-born Hispanic mothers.

**RESULTS:** Hispanic mothers born in Mexico/Central America were more likely to deliver babies with spina bifida (OR = 1.53) than their U.S.-born counterparts. Also, mothers born in Mexico/Central America or who were recent United States immigrants ( $\leq 5$  years) were less likely to deliver babies with all atrial septal defects combined, all septal defects combined, or atrial septal defect, secundum type. However, Hispanic foreign-born mothers who lived in the United States for  $>5$  years were more likely to deliver babies with all neural tube defects combined (OR = 1.42), spina bifida (OR = 1.89), and longitudinal limb defects (OR = 2.34). Foreign-born mothers, regardless of their number of years lived in the United States, were more likely to deliver babies with anotia or microtia.

**CONCLUSIONS:** Depending on the type of birth defect, foreign-born Hispanic mothers might be at higher or lower risk of delivering babies with the defects. The differences might reflect variations in predisposition, cultural norms, behavioral characteristics, and/or ascertainment of the birth defects. Birth Defects Research (Part A), 2009. © 2009 Wiley-Liss, Inc.

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Strickland MJ, Klein M, Correa A, Reller MD, Mahle WT, Riehle-Colarusso TJ, Botto LD, Flanders WD, Mulholland JA, Siffel C, Marcus M, Tolbert PE.

**Ambient air pollution and cardiovascular malformations in Atlanta, Georgia, 1986-2003.** Am J Epidemiol. 2009 Apr 15; 169(8):1004-14. Epub 2009 Mar 3.

Department of Environmental and Occupational Health, Rollins School of Public Health, Emory University, Atlanta, Georgia 30322, USA. mjstric@sph.emory.edu

Associations between ambient air pollution levels during weeks 3-7 of pregnancy and risks of cardiovascular malformations were investigated among the cohort of pregnancies reaching at least 20 weeks' gestation that were conceived during January 1, 1986-March 12, 2003, in Atlanta, Georgia. Surveillance records obtained from the Metropolitan Atlanta Congenital Defects Program, which conducts active, population-based surveillance on this cohort, were reviewed to classify cardiovascular malformations. Ambient 8-hour maximum ozone and 24-hour average carbon monoxide, nitrogen dioxide, particulate matter with an average aerodynamic diameter of  $<10$  microm (PM(10)), and sulfur dioxide measurements were obtained from centrally located stationary monitors. Temporal associations between these pollutants and daily risks of secundum atrial septal defect, aortic coarctation, hypoplastic left heart syndrome, patent ductus arteriosus, valvar pulmonary stenosis, tetralogy of Fallot, transposition of the great arteries, muscular ventricular septal defect, perimembranous ventricular septal defect, conotruncal defects, left ventricular outflow tract defect, and right ventricular outflow defect were modeled by using Poisson generalized linear models. A statistically significant association was observed between PM(10) and patent ductus arteriosus (for an interquartile range increase in PM(10) levels, risk ratio = 1.60, 95% confidence interval: 1.11, 2.31). Of the 60 associations examined in the primary analysis, no other significant associations were observed.

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Strickland MJ, Klein M, Darrow L, Flanders WD, Correa A, Marcus M, Tolbert P.

**The Issue of Confounding in Epidemiological Studies of Ambient Air Pollution and Pregnancy Outcomes.**

J Epidemiol Community Health. 2009 Feb 19. [Epub ahead of print]

United States;

Relationships between ambient air pollution levels during pregnancy and adverse pregnancy outcomes have been investigated using one of three analytic approaches: ambient pollution levels have been contrasted over space, time, or both space and time. Although the three approaches share a common goal, to estimate the causal effects of pollution on pregnancy outcomes, they face different challenges with respect to confounding. In spatial analyses, risk factors that are spatially correlated with pollution levels are confounders; the primary challenges relate to the availability and validity of risk factor measurements. In temporal analyses, where smooth functions of time are commonly used to control for confounding, concerns relate to the adequacy of control and the possibility that abrupt changes in risk might be systematically related to pollution levels. Spatial-temporal approaches are subject to challenges faced in both spatial and temporal analyses. Thoughtful consideration of issues related to confounding is warranted because the causal effects of ambient air pollution on adverse pregnancy outcomes, if they exist, are likely to be small. We present a framework based on counterfactual effect definitions to examine issues related to confounding in spatial, temporal, and spatial-temporal analyses of air pollution and pregnancy outcomes, and we discuss their implications for inference.

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Gilboa SM, Strickland MJ, Olshan AF, Werler MM, Correa A; National Birth Defects Prevention Study.

**Use of antihistamine medications during early pregnancy and isolated major malformations.**

Birth Defects Res A Clin Mol Teratol. 2009 Feb; 85(2):137-50.

National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 1600 Clifton Rd., Atlanta, GA 30333, USA.

**BACKGROUND:** Antihistamines are commonly used during pregnancy. There is little evidence that they have teratogenic effects, but there are knowledge gaps with respect to newer products, as well as the relationship between specific antihistamines and specific birth defects.

**METHODS:** Using the National Birth Defects Prevention Study (1997-2003), the authors examined associations between maternal use of 14 antihistamines during early pregnancy and 26 isolated major birth defects. A Bayesian analysis incorporating prior knowledge about the relationships between antihistamines, birth defects, and measured covariates was conducted.

**RESULTS:** Of the 364 associations investigated, 24 had 95% posterior intervals excluding 1.0. All 24 associations were positive; 23 associations were of weak to moderate magnitude (posterior OR < 3.0) and one was strong (OR > 6.0) but very imprecise. Of the 24 associations, 20 were with noncardiac defects. Eight associations involved the antihistamine diphenhydramine.

**CONCLUSIONS:** The results of this study generally were consistent with no association between birth defects and antihistamine use during early pregnancy. Several of the findings might warrant further investigation, although the observed elevated associations should be interpreted in the context of the number of associations investigated and the analysis of retrospective, self-reported data. © 2009 Wiley-Liss, Inc.

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Carmichael SL, Yang W, Correa A, Olney RS, Shaw GM; National Birth Defects Prevention Study.

**Hypospadias and intake of nutrients related to one-carbon metabolism.**

J Urol. 2009 Jan; 181(1):315-21; discussion 321. Epub 2008 Nov 14.

California Research Division, March of Dimes Foundation, Oakland, California, USA.  
scarmichael@marchofdimes.com

**PURPOSE:** We examined whether hypospadias is associated with maternal intake of folic acid containing vitamin/mineral supplements or dietary intake of nutrients related to one-carbon metabolism (folate, choline, vitamins B12 and B6, thiamine, riboflavin, methionine and zinc).

**MATERIALS AND METHODS:** The study included births from October 1997 to December 2003 that were part of the National Birth Defects Prevention Study. Diet was assessed by food frequency questionnaire during maternal telephone interviews. Analyses included 915 cases

with second or third degree hypospadias (urethra opened at the penile shaft, scrotum or perineum) and 2,266 male, liveborn, nonmalformed controls. All ORs and 95% CIs were estimated from logistic regression models that included several potential confounders. Nutrient based analyses also included energy intake.

**RESULTS:** Hypospadias risk was not associated with supplement use (adjusted ORs were 1.2, 95% CI 0.9-1.6 for intake beginning in the month before or the first month of pregnancy and 1.1, 95% CI 0.8-1.4 for intake beginning in the second or third month, relative to no intake). Among women who took supplements reduced hypospadias risk was associated with higher dietary intakes of choline, methionine and vitamin B12. The respective ORs (CIs) for the highest vs lowest quartiles were 0.7 (0.5-1.1), 0.6 (0.4-0.9) and 0.7 (0.5-1.0). Among women who did not take supplements increased risk of hypospadias was associated with higher vitamin B12 intake. The OR (CI) for the highest vs lowest quartile was 3.1 (1.1-9.0).

**CONCLUSIONS:** This study suggests an association of hypospadias with intake of certain nutrients related to one-carbon metabolism.

\* \* \*

Strickland MJ, Riehle-Colarusso TJ, Jacobs JP, Reller MD, Mahle WT, Botto LD, Tolbert PE, Jacobs ML, Lacour-Gayet FG, Tchervenkov CI, Mavroudis C, Correa A.

**The importance of nomenclature for congenital cardiac disease: implications for research and evaluation.**

Cardiol Young. 2008 Dec;18 Suppl 2:92-100.

National Center on Birth Defects and Developmental Disabilities, US Centers for Disease Control and Prevention, Atlanta, Georgia 30333, USA. MStrickland@cdc.gov

**BACKGROUND:** Administrative databases are often used for congenital cardiac disease research and evaluation, with little validation of the accuracy of the diagnostic codes. **METHODS:** Metropolitan Atlanta Congenital Defects Program surveillance records were reviewed and classified using a version of the International Pediatric and Congenital Cardiac Code. Using this clinical nomenclature as the referent, we report the sensitivity and false positive fraction (1 - positive predictive value) of the International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes for tetralogy of Fallot, transposition of the great arteries, and hypoplastic left heart syndrome.

**RESULTS:** We identified 4918 infants and fetuses with congenital cardiac disease from the surveillance records. Using only the International Classification of Diseases diagnosis codes, there were 280 records with tetralogy, 317 records with transposition, and 192 records with hypoplastic left heart syndrome. Based on the International Pediatric and Congenital Cardiac Code, 330 records were classified as tetralogy, 163 records as transposition, and 179 records as hypoplastic left heart syndrome. The sensitivity of International Classification of Diseases diagnosis codes was 83% for tetralogy, 100% for transposition, and 95% for hypoplastic left heart syndrome. The false positive fraction was 2% for tetralogy, 49% for transposition, and 11% for hypoplastic left heart syndrome.

**CONCLUSIONS:** Analyses based on International Classification of Diseases diagnosis codes may have substantial misclassification of congenital heart disease. Isolating the major defect is difficult, and certain codes do not differentiate between variants that are clinically and developmentally different.

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Reller MD, Strickland MJ, Riehle-Colarusso T, Mahle WT, Correa A.

**Prevalence of congenital heart defects in metropolitan Atlanta, 1998-2005.**

J Pediatr. 2008 Dec; 153(6):807-13. Epub 2008 Jul 26.

Oregon Health and Science University, Portland, OR, USA.

**OBJECTIVE:** To determine an accurate estimate of the prevalence of congenital heart defects (CHD) using current standard diagnostic modalities.

**STUDY DESIGN:** We obtained data on infants with CHD delivered during 1998 to 2005 identified by the Metropolitan Atlanta Congenital Defects Program, an active, population-based, birth defects surveillance system. Physiologic shunts in infancy and shunts associated with

prematurity were excluded. Selected infant and maternal characteristics of the cases were compared with those of the overall birth cohort.

**RESULTS:** From 1998 to 2005 there were 398 140 births, of which 3240 infants had CHD, for an overall prevalence of 81.4/10 000 births. The most common CHD were muscular ventricular septal defect, perimembranous ventricular septal defect, and secundum atrial septal defect, with prevalence of 27.5, 10.6, and 10.3/10 000 births, respectively. The prevalence of tetralogy of Fallot, the most common cyanotic CHD, was twice that of transposition of the great arteries (4.7 vs 2.3/10 000 births). Many common CHD were associated with older maternal age and multiple-gestation pregnancy; several were found to vary by sex.

**CONCLUSIONS:** This study, using a standardized cardiac nomenclature and classification, provides current prevalence estimates of the various CHD subtypes. These estimates can be used to assess variations in prevalence across populations, time, or space.

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Jurczyk P, Lu JJ, Xiong L, Cragan JD, Correa A.

**FRIL: A Tool for Comparative Record Linkage.**

AMIA Annu Symp Proc. 2008 Nov 6:440-4.

Emory University.

A fine-grained record integration and linkage tool (FRIL) is presented. The tool extends traditional record linkage tools with a richer set of parameters. Users may systematically and iteratively explore the optimal combination of parameter values to enhance linking performance and accuracy. Results of linking a birth defects monitoring program and birth certificate data using FRIL show 99% precision and 95% recall rates when compared to results obtained through handcrafted algorithms, and the process took significantly less time to complete. Experience and experimental result suggest that FRIL has the potential to increase the accuracy of data linkage across all studies involving record linkage. In particular, FRIL will enable researchers to assess objectively the quality of linked data.

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Kucik JE, Bitsko RH, Williams L, Lazarus C, Jarman DW, Correa A.

**Birth Defects Cluster Study: a national approach to birth defects cluster investigations.**

Birth Defects Res A Clin Mol Teratol. 2008 Nov; 82(11):805-11.

Division of Birth Defects and Developmental Disabilities, National Center on Birth Defects and Developmental Disabilities, Atlanta, Georgia 30333, USA. jkucik@cdc.gov

**BACKGROUND:** Investigations of clusters of birth defects have been challenging endeavors that have had only modest success identifying causes or risk factors. Some of the challenges to individual cluster investigations have been small sample size and limited data collection. We describe a novel approach for investigating and analyzing pooled information from a series of birth defects cluster investigations.

**METHODS:** The Birth Defects Cluster Study uses a case-control study design with standardized methods, including a case definition, control selection, data collection methods, and data collected (e.g., maternal interviews, blood samples, and environmental samples). Analyses of pooled data from several clusters of the same defect are conducted for specific hypotheses once a sufficient sample size has been achieved. The feasibility of conducting individual birth defect investigations was evaluated on a cluster of gastroschisis.

**RESULTS:** The pilot investigation of a cluster of gastroschisis demonstrated success in recruiting participants and in collecting data and specimens for eventual inclusion in a pooled analysis.

**CONCLUSIONS:** The Birth Defects Cluster Study offers a unique and effective approach to cluster investigations that improves the likelihood of identifying genetic and environmental causes of birth defects and provides a model for cluster investigations of other noninfectious health outcomes.

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Shin M, Besser LM, Correa A.

**Prevalence of spina bifida among children and adolescents in metropolitan Atlanta.**

Birth Defects Res A Clin Mol Teratol. 2008 Nov; 82(11):748-54.

National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia 30333, USA. mshin@cdc.gov

**BACKGROUND:** Although studies have examined the prevalence of spina bifida (SB) among births, little is known about the SB prevalence among children and adolescents. We estimated the prevalence of SB among children and adolescents in metropolitan Atlanta.

**METHODS:** This study used data from a population-based registry of birth defects, with information on children with SB (cases) born in five Atlanta counties from 1979-2002. The population at risk was derived from United States Census data and variations in SB prevalence were examined by race/ethnicity, sex, lesion level, age group under 20 years, 4-year birth cohort, and time period using Poisson regression.

**RESULTS:** From 1979 to 2002, SB birth prevalence decreased from 6.3 to 3.2 per 10,000 live births ( $p < 0.001$ ) and SB prevalence within each age group also declined. In 2002, there were 211 children 0-19 years old surviving with SB in Atlanta (2.4 per 10,000 children 0-19 years old); prevalence of SB was higher among non-Hispanic whites and among children with lumbosacral lesion but did not vary by sex. With the exception of the most recent birth cohort (1998-2002), within each 4-year birth cohort, the prevalence of SB was generally higher among non-Hispanic whites than among non-Hispanic blacks.

**CONCLUSIONS:** This study provides minimum prevalence estimates among children and adolescents with SB in metropolitan Atlanta, and identifies race/ethnic disparities in such prevalence estimates. This information could be useful for assessing the specialized health care needs for children with SB and the possible reasons for the racial/ethnic variation in prevalence of SB.

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Duke W, Williams L, Correa A.

**Using active birth defects surveillance programs to supplement data on fetal death reports: improving surveillance data on stillbirths.**

Birth Defects Res A Clin Mol Teratol. 2008 Nov; 82(11):799-804.

Division of Birth Defects and Developmental Disabilities, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia 30333, USA. cduke@cdc.gov

**BACKGROUND:** Surveillance of stillbirths using fetal death reports (FDRs) has been challenging because of under-reporting of fetal deaths and missing data on the FDRs. Using active case finding and chart abstraction within the infrastructure of established birth defect surveillance programs could potentially enhance the data from FDRs. The data collection form for the Metropolitan Atlanta Congenital Defects Program, an active, population-based birth defects surveillance system, was modified to collect additional information on stillbirths from medical records.

**METHODS:** The study population was a 25% simple random sample of stillbirths recorded on FDRs in 2004 ( $n = 125$ ) by residents in the five central counties of metropolitan Atlanta. Stillbirth was defined as a fetal death at  $> \text{ or } = 20$  weeks gestation or  $> \text{ or } = 350$  g if age was unknown. Data on demographic characteristics and risk factors collected from the two sources were compared for completeness and agreement, as well as causes of and conditions associated with the fetal death.

**RESULTS:** Combining data sources provided more information. Demographic and risk factor variables in the two data sources showed strong agreement (categorical variable, kappa range = 0.79-1.00; continuous variable, correlation coefficient range = 0.61-1.00). The actively ascertained data provided more complete information for causes and conditions of fetal death. Data from the FDRs yielded 42% of cases with no listed cause of death or associated condition compared with 10% using Metropolitan Atlanta Congenital Defects Program data.

**CONCLUSIONS:** Expanding the potential of existing active birth defects surveillance programs to include stillbirth surveillance could potentially improve the quantity and quality of available data on fetal deaths. Ongoing studies are needed to corroborate these findings and to assess completeness of case ascertainment.

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Jurczyk P, Lu JJ, Xiong L, Cragan JD, Correa A.

**Fine-grained record integration and linkage tool.**

Birth Defects Res A Clin Mol Teratol. 2008 Nov; 82(11):822-9.

National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia 30322, USA. pjurczy@emory.edu

**BACKGROUND:** As part of the surveillance program to monitor the occurrence of birth defects in the metropolitan Atlanta area, we developed a record linkage software tool that provides latitude in the choice of linkage parameters, allows for efficient and accurate linkages, and enables objective assessments of the quality of the linked data.

**METHODS:** We developed and implemented a Java-based fine-grained probabilistic record integration and linkage tool (FRIL) that incorporates a rich collection of record distance metrics, search methods, and analysis tools. Along its workflow, FRIL provides a rich set of user-tunable parameters augmented with graphic visualization tools to assist users in understanding the effects of parameter choices. We used this software tool to link data from vital records (n = 1.25 million) with birth defects surveillance records (n = 12,700) from the metropolitan Atlanta Congenital Defects Program (MACDP) for the birth years 1967-2006.

**RESULTS:** Compared with the data linkage performed by conventional algorithms, the data linkage of birth certificates with birth defect records in MACDP using FRIL was more efficient. The linkage based on FRIL was also accurate, showing 99% precision and 95% recall. Based on positive user feedback, new features continue to be developed, and the tool is being adopted in several other data linkage projects in MACDP.

**CONCLUSIONS:** A software tool that allows significant user interaction and control, such as FRIL, can provide accurate data linkages for birth defect surveillance programs and allows an objective assessment of the quality of linked data.

## **USA-Texas: BDES - CANFIELD MA**

Ramadhani T, Short V, Canfield MA, Waller DK, Correa A, Royle M, Scheuerle A; National Birth Defects Prevention Study (NBDPS).

**Are birth defects among Hispanics related to maternal nativity or number of years lived in the United States?**

Birth Defects Res A Clin Mol Teratol. 2009 Apr 6. [Epub ahead of print]

Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, Texas.

**BACKGROUND:** Literature on the risk of birth defects among foreign- versus U.S.-born Hispanics is limited or inconsistent. We examined the association between country of birth, immigration patterns, and birth defects among Hispanic mothers.

**METHODS:** We used data from the National Birth Defects Prevention Study and calculated odds ratios (ORs) and 95% confidence intervals and assessed the relationship between mothers' country of birth, years lived in the United States, and birth defects among 575 foreign-born compared to 539 U.S.-born Hispanic mothers.

**RESULTS:** Hispanic mothers born in Mexico/Central America were more likely to deliver babies with spina bifida (OR = 1.53) than their U.S.-born counterparts. Also, mothers born in Mexico/Central America or who were recent United States immigrants ( $\leq 5$  years) were less likely to deliver babies with all atrial septal defects combined, all septal defects combined, or atrial septal defect, secundum type. However, Hispanic foreign-born mothers who lived in the United States for  $>5$  years were more likely to deliver babies with all neural tube defects combined (OR = 1.42), spina bifida (OR = 1.89), and longitudinal limb defects (OR = 2.34). Foreign-born mothers, regardless of their number of years lived in the United States, were more likely to deliver babies with anotia or microtia.

**CONCLUSIONS:** Depending on the type of birth defect, foreign-born Hispanic mothers might be at higher or lower risk of delivering babies with the defects. The differences might reflect

variations in predisposition, cultural norms, behavioral characteristics, and/or ascertainment of the birth defects. Birth Defects Research (Part A), 2009. © 2009 Wiley-Liss, Inc.

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**Canfield MA**, Ramadhani TA, Shaw GM, Carmichael SL, Waller DK, Mosley BS, Royle MH, Olney RS; The National Birth Defects Prevention Study.

**Anencephaly and spina bifida among Hispanics: Maternal, sociodemographic, and acculturation factors in the National Birth Defects Prevention Study.**

Birth Defects Res A Clin Mol Teratol. 2009 Mar 30. [Epub ahead of print]

Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, Texas.

**BACKGROUND:** We used data from the multisite National Birth Defects Prevention Study for expected delivery dates from October 1997 through 2003, to determine whether the increased risk in anencephaly and spina bifida (neural tube defects (NTDs)) in Hispanics was explained by selected sociodemographic, acculturation, and other maternal characteristics.

**METHODS:** For each type of defect, we examined the association with selected maternal characteristics stratified by race/ethnicity and the association with Hispanic parents' acculturation level, relative to non-Hispanic whites. We used logistic regression and calculated crude odds ratios (ORs) and their 95% confidence intervals (Cis).

**RESULTS:** Hispanic mothers who reported the highest level of income were 80% less likely to deliver babies with spina bifida. In addition, highly educated Hispanic and white mothers had 76 and 35% lower risk, respectively. Other factors showing differing effects for spina bifida in Hispanics included maternal age, parity, and gestational diabetes. For spina bifida there was no significant elevated risk for U.S.-born Hispanics, relative to whites, but for anencephaly, corresponding ORs ranged from 1.9 to 2.3. The highest risk for spina bifida was observed for recent Hispanic immigrant parents from Mexico or Central America residing in the United States <5 years (OR = 3.28, 95% CI = 1.46-7.37).

**CONCLUSIONS:** Less acculturated Hispanic parents seemed to be at highest risk of NTDs. For anencephaly, U.S.-born and English-speaking Hispanic parents were also at increased risk. Finally, from an etiologic standpoint, spina bifida and anencephaly appeared to be etiologically heterogeneous from these analyses. Birth Defects Research (Part A), 2009. ©2009 Wiley-Liss, Inc.

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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. 2009 Mar; 13(2):274-85. Epub 2008 Mar 4.

Texas Department of State Health Services, Birth Defects Epidemiology and Surveillance Branch, 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.

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Browne ML, Rasmussen SA, Hoyt AT, Waller DK, Druschel CM, Caton AR, **Canfield MA**, Lin AE, Carmichael SL, Romitti PA; and the National Birth Defects Prevention Study.

**Maternal thyroid disease, thyroid medication use, and selected birth defects in the National Birth Defects Prevention Study.**

Birth Defects Res A Clin Mol Teratol. 2009 Feb 12. [Epub ahead of print]

Congenital Malformations Registry, New York State Department of Health, Troy, New York.

**BACKGROUND:** Although thyroid disorders are present in approximately 3% of pregnant women, little is known about the association between maternal thyroid disease and birth defects.

**METHODS:** We assessed the association between maternal thyroid disease, thyroid medication use, and 38 types of birth defects among 14,067 cases and 5875 controls in the National Birth Defects Prevention Study, a multisite, population-based, case-control study. Infants in this study were born between October 1997 and December 2004. Information on exposures including maternal diseases and use of medications was collected by telephone interview.

**RESULTS:** We found statistically significant associations between maternal thyroid disease and left ventricular outflow tract obstruction heart defects (1.5; 95% CI, 1.0-2.3), hydrocephaly (2.9; 95% CI, 1.6-5.2), hypospadias (1.6; 95% CI, 1.0-2.5), and isolated anorectal atresia (2.4; 95% CI, 1.2-4.6). Estimates for the association between periconceptional use of thyroxine and specific types of birth defects were similar to estimates for any thyroid disease. Given that antithyroid medication use was rare, we could not adequately assess risks for their use for most case groups.

**CONCLUSIONS:** Our results are consistent with the positive associations between maternal thyroid disease or thyroid medication use and both hydrocephaly and hypospadias observed in some previous studies. New associations with left ventricular outflow tract obstruction heart defects and anorectal atresia may be chance findings. Birth Defects Research (Part A), 2009. © 2009 Wiley-Liss, Inc.

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Felkner M, Suarez L, **Canfield MA**, Brender JD, Sun Q.

**Maternal serum homocysteine and risk for neural tube defects in a Texas-Mexico border population.**

Birth Defects Res A Clin Mol Teratol. 2009 Jan 29. [Epub ahead of print]

Texas Department of State Health Services, Austin, Texas.

**BACKGROUND::** To better understand the neural tube defect (NTD) causal pathway, the authors measured homocysteine, an indicator of tissue micronutrient deficiencies. The authors examined independent and joint associations of serum homocysteine, B(12,) and folate and red blood cell (RBC) folate with NTD-affected pregnancies.

**METHODS::** Case women in this population-based study had NTD-affected pregnancies and resided and delivered in one of the 14 Texas-Mexico border counties from 1995 through 2000. Control women were study area residents delivering normal live births during the same period. The authors measured homocysteine levels using tandem mass spectroscopy; competitive binding was used for other biomarkers.

**RESULTS::** Homocysteine testing was done on 103 cases and 139 controls. Odds ratios (ORs) were increased in all upper homocysteine quintiles compared to the lowest quintile (1.7, 1.3, 2.8, 2.4). Women with high homocysteine values had increased ORs regardless of high versus low levels for B(12) (OR = 3.5, 4.8, respectively) or RBC folate (OR = 2.9, 3.5, respectively).

CONCLUSIONS:: High serum homocysteine levels are associated with NTD-affected pregnancies. Moreover, high homocysteine levels have a detrimental effect on NTD-risk even when serum B(12) or RBC folate levels are high. Excess homocysteine might play an independent role in the development of NTDs. Birth Defects Research (Part A), 2009. © 2009 Wiley-Liss, Inc.

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Mosley BS, Cleves MA, Siega-Riz AM, Shaw GM, **Canfield MA**, Waller DK, Werler MM, Hobbs CA; National Birth Defects Prevention Study.

**Neural tube defects and maternal folate intake among pregnancies conceived after folic acid fortification in the United States.**

Am J Epidemiol. 2009 Jan 1; 169(1):9-17. Epub 2008 Oct 25.

Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children's Hospital Research Institute, Little Rock, Arkansas 72202, USA.

Rates of neural tube defects have decreased since folic acid fortification of the food supply in the United States. The authors' objective was to evaluate the associations between neural tube defects and maternal folic acid intake among pregnancies conceived after fortification. This is a multicenter, case-control study that uses data from the National Birth Defects Prevention Study, 1998-2003. Logistic regression was used to compute crude and adjusted odds ratios between cases and controls assessing maternal periconceptional use of folic acid and intake of dietary folic acid. Among 180 anencephalic cases, 385 spina bifida cases, and 3,963 controls, 21.1%, 25.2%, and 26.1%, respectively, reported periconceptional use of folic acid supplements. Periconceptional supplement use did not reduce the risk of having a pregnancy affected by a neural tube defect. Maternal intake of dietary folate was not significantly associated with neural tube defects. In this study conducted among pregnancies conceived after mandatory folic acid fortification, the authors found little evidence of an association between neural tube defects and maternal folic acid intake. A possible explanation is that folic acid fortification reduced the occurrence of folic acid-sensitive neural tube defects. Further investigation is warranted to possibly identify women who remain at increased risk of preventable neural tube defects.

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**Canfield MA**, Marengo L, Ramadhani TA, Suarez L, Brender JD, Scheuerle A.

**The prevalence and predictors of anencephaly and spina bifida in Texas.**

Paediatr Perinat Epidemiol. 2009 Jan; 23(1):41-50.

Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX, USA.

Texas shares a 1255-mile border with Mexico and encompasses a variety of ecosystems, industries and other potential environmental exposures. The Texas Birth Defects Registry is an active surveillance system which covers all pregnancy outcomes (livebirths, fetal deaths and elective pregnancy terminations). This study describes the occurrence and the predictors of neural tube defects (anencephaly and spina bifida) in Texas between 1999 and 2003. Birth prevalence, crude and adjusted prevalence ratios and 95% confidence intervals were calculated using Poisson regression, for each defect, by fetal/infant sex, delivery year and maternal sociodemographic characteristics. Among approximately 1.8 million livebirths, a total of 1157 neural tube defects cases were ascertained by the Registry, resulting in an overall prevalence of 6.33 cases per 10 000 livebirths. The prevalences of anencephaly and spina bifida were 2.81 and 3.52 per 10 000 livebirths respectively. Prevalences of both defects were highest in Hispanics, among mothers living along the border with Mexico, among women of higher parity and among mothers who were 40+ years of age. In addition, the prevalence of each defect was higher among women with no record of prenatal care and among women with less than 7 years of education. Hispanic ethnicity was an important predictor for anencephaly, along with sex, maternal age, parity and border residence. However, only border residence and delivery year were significant predictors for spina bifida.

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Case AP, Canfield MA, Barnett A, Raimondo P, Drummond-Borg M, Livingston J, Kowalik J.  
**Proximity of pediatric genetic services to children with birth defects in Texas.**  
Birth Defects Res A Clin Mol Teratol. 2008 Nov; 82(11):795-8.

Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, Texas 78714-9347, USA. amy.case@dshs.state.tx.us

**BACKGROUND:** Families of children with major structural malformations often benefit greatly from genetic services. However, these services may not be readily available in all areas. The purpose of this study was to use data from a statewide birth defects registry and geographic information system methodology to compare the spatial distribution and to summarize the distance of pediatric clinical genetic service providers in relation to residential addresses of children with selected birth defects in Texas.

**METHODS:** Live-born children delivered between 1999-2004 in the Texas Birth Defects Registry with major structural defects and chromosomal anomalies were selected by a clinical geneticist according to diagnosis code. Mother's address at delivery of the case infants was geocoded as was the location of offices where clinical geneticists in Texas see pediatric patients. Using geographic information system tools, the authors then computed distance from each case mother's residence to the location of the nearest office where pediatric patients can be seen by clinical geneticists, summarized these distances, and graphically plotted the location of each case in relation to the nearest provider.

**RESULTS:** Nearly 25,000 Registry cases met the criteria for selection for geocoding. Of those, 22,875 (91.8%) were successfully geocoded to street level.

**CONCLUSIONS:** Although 82% of addresses were within 30 miles of the nearest pediatric genetic clinic, 14% lived 31-100 miles from the nearest facility, and 4% of case families would need to drive more than 100 miles, including some who live in midsized cities, indicating geographic disparities in access to these necessary services.

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Wang J, Waller DK, Hwang LY, Taylor LG, Canfield MA.

**Prevalence of infantile hypertrophic pyloric stenosis in Texas, 1999-2002.**

Birth Defects Res A Clin Mol Teratol. 2008 Nov; 82(11):763-7.

The University of Texas, Houston Health Science Center, School of Public Health, Houston, Texas 77030, USA.

**BACKGROUND:** The cause of infantile hypertrophic pyloric stenosis (IHPS) is poorly understood. This descriptive study of IHPS focuses on the effect of maternal nativity, maternal Hispanic ethnicity, subtypes of maternal Asian ethnicity, and the timing of the infant's surgery, that is, pyloromyotomy.

**METHODS:** All cases of IHPS born in Texas from 1999 through 2002 were retrieved from the Texas Birth Defects Registry. Crude prevalence ratios and adjusted prevalence ratios (aPRs) were calculated using logistic regression.

**RESULTS:** IHPS occurred predominantly in boys (aPR 4.21; 95% CI: 3.81, 4.65) compared with girls. Compared with Whites, there was a lower prevalence among Blacks (aPR 0.36; 95% CI: 0.30, 0.43), foreign-born Hispanics (aPR 0.61; 95% CI: 0.54, 0.69), Chinese (aPR 0.11; 95% CI: 0.01, 0.78), Vietnamese (aPR 0.17; 95% CI: 0.06, 0.46), Asian Indians (aPR 0.33; 95% CI: 0.15, 0.75), and Filipinos (aPR 0.22; 95% CI: 0.05, 0.91). In aggregate, foreign born Asians had a decreased risk of IHPS (aPR 0.20; 95% CI: 0.11, 0.37) compared to Whites. We observed no decrease in the risk of IHPS among US-born Asians (in aggregate) or US-born Hispanics. The strength of these risk factors did not vary according to the timing of the pyloromyotomy.

**CONCLUSIONS:** This study confirmed previous findings that female infants and Black infants have a lower rate of IHPS. Large decreases in rates of IHPS were observed among foreign-born Hispanics and foreign-born Asians, but not among their US-born counterparts. These findings may be explained by differences in the frequency of behavioral risk factors for IHPS or differences in the frequency of ascertainment of mild cases of IHPS by ethnicity or nativity.

## USA-Utah: UBDN - FELDKAMP M

Collier SA, Rasmussen SA, Feldkamp ML, Honein MA; National Birth Defects Prevention Study. **Prevalence of self-reported infection during pregnancy among control mothers in the National Birth Defects Prevention Study.**

Birth Defects Res A Clin Mol Teratol. 2009 Mar; 85(3):193-201.

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**BACKGROUND:** Although specific maternal infections during pregnancy have been associated with birth defects and other adverse pregnancy outcomes, the prevalence of infections during pregnancy has not been well described.

**METHODS:** We estimated the prevalence of self-reported infection among 4967 women with live-born infants without major birth defects. We assessed the prevalence of reported infections and fever by type of infection, specific illness, and maternal characteristics including race and age.

**RESULTS:** Overall, 63.6% of women reported at least one infection during pregnancy. Reports of infections were more common during pregnancy than in the 3 months before pregnancy. Nearly half (49.6%) of women reported a respiratory infection, 20.5% reported a fever, 17.1% reported a urinary tract infection, 4.2% reported a yeast infection, and 3.4% reported a sexually transmitted disease. A subanalysis of self-reported infection and preterm delivery was performed among primiparous mothers with singleton pregnancies, but no statistically significant differences in infection prevalence were found. Women younger than 35 years reported nonrespiratory infections more frequently than women aged 35 years or older (prevalence ratio [PR] 1.41; 95% confidence interval [CI]: 1.21-1.64). Prevalence of nonrespiratory infections was also higher among those who smoked than among those who did not (PR 1.33; 95% CI: 1.20-1.47).

**CONCLUSIONS:** Reported infections during pregnancy are common, implying that a small increase in risk for birth defects or other adverse pregnancy outcomes could have a significant public health effect and underscoring the importance of understanding the effects of prenatal infections. © 2009 Wiley-Liss, Inc.

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Munger RG, Tamura T, Johnston KE, Feldkamp ML, Pfister R, Carey JC.

**Plasma zinc concentrations of mothers and the risk of oral clefts in their children in Utah.**

Birth Defects Res A Clin Mol Teratol. 2009 Feb; 85(2):151-5.

Department of Nutrition and Food Sciences, Utah State University, Logan, UT, USA.

**BACKGROUND:** The role of maternal zinc nutrition in human oral clefts (OCs) is unclear. We measured plasma zinc concentrations (PZn) of case and control mothers to evaluate the associations between PZn and risk of OCs with and without other malformations.

**METHODS:** Case mothers were ascertained by the Utah Birth Defects Network and control mothers were selected from Utah birth certificates by matching for child gender and delivery month and year. Maternal blood was collected >1 year after the last pregnancy. PZn was available for 410 case mothers who were divided into four subgroups: isolated cleft lip with or without cleft palate (CL/P-I, n = 231), isolated cleft palate (CP-I, n = 74), CL/P with other malformations (CLP-M, n = 42), and CP with other malformations (CP-M, n = 63). PZn was available for 447 control mothers. The mean age of children at blood sampling was 3.7 years for all cases combined and 4.3 years for controls.

**RESULTS:** Mean PZns of all groups were similar, and low PZn (<11.0 micromol/L) was found in 59% of cases and 62% of controls. Risk of OCs did not vary significantly across PZn quartiles for the four subgroups individually and all OC groups combined.

**CONCLUSIONS:** We previously reported that poor maternal zinc status was a risk factor for OCs in the Philippines, where OC prevalence is high and maternal PZn is low. In Utah, however, no such association was found, suggesting that poor maternal zinc status may become a risk factor only when zinc status is highly compromised. © 2008 Wiley-Liss, Inc.

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**Feldkamp ML**, Alder SC, Carey JC.

**A case control population-based study investigating smoking as a risk factor for gastroschisis in Utah, 1997-2005.**

Birth Defects Res A Clin Mol Teratol. 2008 Nov; 82(11):768-75.

Department of Medical Genetics, University of Utah Health Sciences Center, Salt Lake City, Utah 84132, USA. Marcia.feldkamp@hsc.utah.edu

**BACKGROUND:** Smoking in pregnancy increases the risk for many different adverse pregnancy outcomes, including birth defects. Gastroschisis, a birth defect most commonly associated with young maternal age has been associated with smoking, but findings are inconsistent. We assessed whether smoking increases the risk for gastroschisis using population-based data from Utah.

**METHODS:** Gastroschisis cases (n = 189) were identified from the Utah Birth Defect Network and all live births without birth defects (n = 423,499) occurring in Utah from January 1, 1997 through December 31, 2005 served as controls. Exposure data were derived from birth certificates and fetal death certificates and, for terminated pregnancies, the Utah Birth Defect Network.

**RESULTS:** Women who smoked during the first trimester of pregnancy had an increased risk of gastroschisis (OR 1.6; 95% CI: 1.1, 2.3) after adjusting for maternal age and preconception BMI. Discordance between birth certificate data and data from structured interviews increased exposure prevalence from 16.9 to 22.2% for case mothers and 7.4 to 13.2% for control mothers. Accounting for this misclassification, the crude OR decreased by 24%, 1.9 (1.3, 2.7).

**CONCLUSIONS:** Though first trimester cigarette smoking was reported on birth certificates by more mothers of gastroschisis cases than controls, adjustment for confounders (maternal age and preconception BMI) and smoking misclassification suggests the association is weak. Despite a decrease in smoking prevalence among all women of childbearing years in Utah between 1997 and 2005, the prevalence of gastroschisis has not followed a similar trend.

## **Wales: CARIS - MORGAN M**

Ch'ng CL, Kingham JG, **Morgan M**.

**Acute fatty liver in pregnancy in the UK.**

Gut. 2009 Mar; 58(3):467; author reply 467-8.