

## **Sudden unexpected death in children with heart disease.**

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*Congenit Heart Dis. 2006 May;1(3):89-97.*

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**OBJECTIVE:** To review a mortality database, and identify all sudden unexpected deaths in patients followed by the cardiac program.

**DESIGN:** Retrospective review of prospectively maintained database.

**RESULTS:** Over 8 years, we identified 80 sudden unexpected deaths, among which there were sufficient data in 69 (24 females). Patients died at a median age of 17.2 months (28 days-18.8 years). Forty-six patients had 2 functional ventricles and 23 had received palliation for a single-functional ventricle. Patients with a single ventricle died at a younger age (median 120 days; 28 days-17.2 years) and sooner after last assessment (median 27 days; 1-146 days) than patients in the biventricular group (median age 2 years; 43 days-18.8 years; median time since last assessment 49 days, 1 days-1 year) ( $P < .01$ ;  $P = .01$ ). Thrombosis was the most common cause (61%) of death in the single-ventricle group. Arrhythmia or presumed arrhythmia was the most common cause (46%) of death in the biventricular group. Fifty-one patients had undergone surgery. Six patients had primary electrophysiological disease, and 5 had cardiomyopathy. Eight deaths occurred in patients with pulmonary vascular disease.

**CONCLUSION:** Our study demonstrates that sudden unexpected death occurred at a frequency of at least 10 patients per year over an 8-year period with 55,730 patient encounters. We were able to determine a clinical cause of death in most patients. Arrhythmias (30%) and pulmonary vascular disease (13%) are important causes of sudden death. Simple aortic valve disease and hypertrophic cardiomyopathy are rare (4%) causes of sudden death in childhood. Infants and young children with surgical shunts comprise 23% of sudden unexpected deaths that occur within a month of the last evaluation. Close surveillance of these patients is warranted.

## **Prone sleeping position increases the risk of SIDS in the day more than at night.**

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*Acta Paediatr. 2008 Mar 28 [Epub ahead of print]*

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**Background:** SIDS mortality is higher during the night than in the day.

**Aim:** (1) To examine risk factors for SIDS by time of day and (2) to see if the proportion of deaths at night has changed from prior to the 'Back to Sleep' campaign, which recommended infants sleep supine.

**Methods:** A large population-based SIDS matched case-control (GeSID) study conducted from 1998 to 2001 (when the prevalence of infants placed prone to sleep was 4.1%). The reference sleep of the controls was matched for the estimated time of death for the case. Risk factors for SIDS were examined for night-time and day-time deaths. The estimated time of death was compared with that from an earlier study in Germany (1990-1994 when prevalence of prone sleeping was 32.2%).

**Results:** There were 333 SIDS cases and 998 matched controls. The increased risk with placed prone to sleep was significantly different during the day [adjusted OR = 18.15 (95% CI = 5.91-55.69)] compared with during the night [adjusted OR = 3.49 (95% CI = 1.46-8.39; p-value for interaction = 0.011)]. There was no significant difference in the other risk factors examined by

time of day in the multivariate analysis. The mean time found dead was 09:07. In the earlier study the mean time found dead was 08:54 and the difference was not significant ( $p = 0.57$ ).

**Conclusions:** This study confirms previous observations that prone sleeping position carries a greater risk during the day than at night. However, the reduction in infants sleeping prone has not been associated with a reduced number of deaths in the day in Germany.

### **Shaken baby syndrome: re-examination of diffuse axonal injury as cause of death.**

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*Acta Neuropathol.* 2008 Mar 26 [Epub ahead of print]

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The discussion surrounding shaken baby syndrome (SBS) arose from the lack of evidence implicating diffuse axonal injury (DAI) as a cause of death. It was assumed instead that injury to the cervical cord, medulla, and nerve roots played a causal role. The present pathomorphological study examines 18 selected infants (<1-year-old) whose deaths were highly suspicious for SBS, exhibiting the classical SBS triad of acute subdural hemorrhage (SDH), retinal bleeding, and encephalopathy. Gross autopsy and microscopic findings of these infants were compared with those of 19 victims of sudden infant death syndrome (SIDS; control group 1) and of 14 infants who died of disease or injuries/violence not involving the head, neck or eyes (control group 2). Symptoms of mechanical impact to the head were evident in seven of the SBS infants, but in none of the control infants. DAI was not detected in either the SBS or control cases. Localized axonal injury (AI) was regularly present in the brains of the SBS infants surviving longer than 1.5-3.0 h, but only occasionally in the craniocervical junction and within the nerve roots of the upper cervical cord; it was never present in the medulla. Epidural hemorrhage of the cervical cord was seen in four of the ten examined SBS cases, but in none of the control cases. Based on the absence of DAI in the brain and of signs of generalized cervical cord or nerve root injuries, we conclude that the cause of death in the SBS victims was a global cerebral ischemia secondary to SDH, focal vasospasm, trauma-induced transitory respiratory and/or circulatory failure.

### **Ethical and logistical considerations of multicenter parental bereavement research.**

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*J Palliat Med.* 2008 May-Jun;11(3):444-50.

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**Background:** Multicenter research has the potential to recruit participants with diverse racial, ethnic, and geographic backgrounds and is essential for understanding heterogeneity in bereavement. The National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN) is a multicenter network charged with conducting research on the pathophysiology and management of critical illness in childhood. Among its research activities, the CPCCRN has undertaken research in parental bereavement because most childhood deaths in the United States occur in hospitals, primarily in critical care units.

**Objective:** The purpose of this paper is to discuss ethical and logistical issues found by the CPCCRN to be problematic to multicenter research with bereaved parents and to explore research strategies that may be practicably implemented.

**Results:** Ethical and logistical challenges encountered by the CPCCRN included issues of privacy; confidentiality; voluntariness; minimizing risks; working with multiple institutional review boards; researcher qualifications, training and support; and methods of data collection. Strategies to address these challenges included local recruitment of participants; flexibility in consent methods across sites; participant options for methods of data collection; involvement of local bereavement support services; central training of researchers with systematic monitoring and opportunities for support; and use of a secure Web-based collaborative workspace.

**Conclusions:** Multicenter parental bereavement research has distinct ethical issues that must be addressed by the logistics of the research plan. Greater attention to the issues identified may facilitate research to reduce adverse mental and physical health outcomes in a diverse population of bereaved individuals.

### **Cytogenetic analysis after evaluation of 750 fetal deaths: proposal for diagnostic workup.**

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Obstet Gynecol. 2008 Apr;111(4):865-74.

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**OBJECTIVE:** To estimate success rates for cytogenetic analysis in different tissues after intrauterine fetal death, and study selection criteria and value of cytogenetic testing in determining cause of death.

**METHODS:** Cytogenetic analyses and the value of this test in determining cause by a multidisciplinary panel were studied in 750 fetal deaths. Morphologic abnormalities, small for gestational age (SGA), advanced maternal age (older than 35 years) and maceration were studied as selection criteria.

**RESULTS:** Chromosomal abnormalities were observed in 13% of fetal deaths. Cytogenetic success rates were significantly higher for invasive testing (85%) than for postpartum tissue analysis (28%,  $P < .001$ ). There were more abnormal chromosomes (38%) in fetal deaths with morphologic abnormalities than in those without (5%,  $P < .001$ ). This was not observed for SGA (16% compared with 9.2%,  $P = .22$ ) or for advanced maternal age (16.7% compared with 12.0%,  $P = .37$ ). The posterior probability of a chromosomal abnormality in the absence of morphologic abnormalities was still 4.6%. Cytogenetic analysis was successful in 35% of severely macerated fetuses. We do not advise using these selection criteria, because the failure rate was high on postpartum tissues. Cytogenetic analysis was valuable in determining the cause in 19% of the fetal deaths.

**CONCLUSION:** Parents should be counseled on aspects of cytogenetic analysis after fetal death. We advise performing nonselective invasive testing after fetal death and before labor for all fetal deaths. LEVEL OF EVIDENCE: II.

### **The influence of the environment and other exogenous agents on spontaneous abortion risk.**

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J Toxicol Environ Health B Crit Rev. 2008 Mar;11(3-4):221-41.

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It is estimated that close to 30% of all pregnancies end in spontaneous abortion. Although about 60% of spontaneous abortions are thought to be due to genetic, infectious, hormonal, and immunological factors, the role of the environment remains poorly understood. Pregnancy involves a delicate balance of hormonal and immunological functions, which may be affected by environmental substances. Many toxic substances that are persistent in the environment and accumulate in the fatty tissues may disrupt this equilibrium. This overview addresses known risk factors for spontaneous abortions and examines the role, if any, that environmental factors (chemical and physical) may play in the etiology of this adverse health outcome.

### **Effect of Gluten-Free Diet on Pregnancy Outcome in Celiac Disease Patients with Recurrent Miscarriages.**

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Dig Dis Sci. 2008 Mar 27 [Epub ahead of print]

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**Purpose:** Available literature data show that celiac disease (CD) is a frequent cause of recurrent miscarriage. However, data are lacking for pregnancy outcome when the patient is on a gluten-free diet (GFD). A case-control study about the effect of GFD on pregnancy was conducted from 1995 to 2006. A cohort of 13 women (mean age 32 years, range 22-38 years) affected by CD with recurrent miscarriages was observed. In all of them several causes of miscarriage (gynecological, endocrine, hematological, etc.) were excluded. All patients were started on a gluten-free diet and were reassessed throughout a long-term follow-up period to evaluate the outcome of pregnancy.

**Results:** Six of 13 became pregnant (46.15%) as follows: 1 patient (7.69%) 1 year after GFD was started, 3 patients (23.07%) 2 years after GFD was started, 1 patient (7.69%) after 3 years, and finally 1 (7.69%) 4 years after GFD was started. Moreover, two patients (16.66%) had multiple pregnancies (one had had two childbirths and another had undergone three births within a 7-year follow-up period under GFD).

**Conclusions:** GFD seems to favor a positive outcome of pregnancy in most CD patients with recurrent miscarriage.

### **Stillbirth in rural Bangladesh: arsenic exposure and other etiological factors: a report from Gonoshasthaya Kendra.**

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Bull World Health Organ. 2008 Mar;86(3):172-7.

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**OBJECTIVE:** To use data collected by Gonoshasthaya Kendra, a large nongovernmental organization providing health care to some 600 villages, to describe the epidemiological pattern of stillbirth and any additional contribution made by arsenic contamination of hand-pump wells in Bangladesh.

**METHODS:** Completed pregnancies and outcomes (n = 30 984) for two calendar years, together with existing data on 26 socioeconomic and health factors were selected for study. The health care in these villages was administered from 16 geographical centres; information on the average arsenic concentration in each centre was obtained from the National Hydrochemical Survey. After univariate analysis, a multivariate, multilevel, logistic model for stillbirth was developed. The additional effect of arsenic was calculated having adjusted for all potential confounders thus identified.

**FINDINGS:** The overall stillbirth rate was 3.4% (1056/30 984) and increased with estimated arsenic concentration (2.96% at < 10 microg/l; 3.79% at 10 microg/l to < 50 microg/l; 4.43% at > 50 microg/l). Having adjusted for 17 socioeconomic and health factors, the odds ratios estimated for arsenic (with < 10 microg/l as reference) remained raised: 1.23 (95% confidence interval, CI: 0.87A1.74) at 10 microg/l to < 50 microg/l and 1.80 (95% CI: 1.14A2.86) at 50 microg/l or greater.

**CONCLUSION:** A increased risk of stillbirth is associated with arsenic contamination. This risk, substantial enough to be detected by an ecological approach and not readily attributable to unmeasured confounding, is essentially preventable and all efforts must be made to protect women at high risk.

### **The fetuses-at-risk approach: clarification of semantic and conceptual misapprehension.**

*Joseph KS.*

BMC Pregnancy Childbirth. 2008 Mar 26;8(1):11 [Epub ahead of print]

**BACKGROUND:** Although proponents of the fetuses-at-risk approach describe it as a causal model that resolves various conundrums, several areas of semantic and conceptual misapprehension remain. Differences in terminology include use of denominators such as 'ongoing pregnancies' and the need for an ad hoc 'correction factor' in order to calculate gestational age-specific rates. Further, there is conceptual disagreement regarding the proper candidates for neonatal death and related phenomena. Perhaps the most egregious misconception is the belief that rising rates of gestational age-specific perinatal mortality observed under the fetuses-at-risk model automatically imply the need for indiscriminate increases in iatrogenic preterm delivery.

**DISCUSSION:** The term 'fetuses at risk' addresses the plurality of candidates for stillbirth in a multi-fetal pregnancy, while the use of standard terminology such as 'cumulative incidence' and 'incidence density' harmonizes the language of perinatal epidemiology with that used in the general epidemiologic literature. On the conceptual side, it is necessary to integrate clinical insights regarding latent periods into models of neonatal morbidity and mortality. The contention that the fetuses-at-risk approach implies the need for indiscriminate iatrogenic preterm delivery is a non-sequitur (just as rising age-specific cancer death rates do not imply the need for routine chemotherapy and radiation for all middle aged people). Finally, the traditional and fetuses-at-risk models are better viewed in terms of function as prognostic (non-causal) and causal models, respectively.

**CONCLUSIONS:** A careful examination of terms and concepts helps situate the traditional perinatal and the fetuses-at-risk approaches within the broader context of non-causal and causal models within general epidemiology.

### **Spontaneous abortions among nickel-exposed female refinery workers.**

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Int J Environ Health Res. 2008 Apr;18(2):99-115.

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A case-control study to investigate whether women employed in nickel-exposed work areas in early pregnancy are at elevated risk of spontaneous abortion (SA). Data about pregnancy outcome and maternal factors were obtained about each delivery and SA from women in selected work places. Each pregnancy record was assigned a categorical nickel (Ni) exposure rating according to the women's occupations at pregnancy onset. The guidelines were the water-soluble Ni subfraction of the inhalable aerosol fraction obtained by personal monitoring for nickel- and

copper-refinery workers or/and measured urinary-Ni concentrations. The unadjusted odds ratio for the association between the maternal exposure to Ni and an SA for Ni-exposed women was 1.38 (95% confidence interval: 1.04-1.84), and the adjusted was 1.14 (0.95-1.37). In conclusion, there was no statistical association between maternal occupational exposure to water-soluble Ni in early pregnancy and the risk of self-reported SA. The findings do not exclude the possibility of a weak excess risk, or a risk in the first weeks of pregnancy.

### **Pregnancy loss after first trimester viability in women with sickle cell trait: a preliminary report.**

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South Med J. 2008 Feb;101(2):150-1.

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**BACKGROUND:** Traditionally, sickle cell trait has not been associated with a higher risk of fetal death, but we noted several, which led us to assess all such pregnancies.

**METHODS:** In this retrospective study, 131 patients with sickle cell trait were analyzed over a two-year period. The Institutional Review Board approved the collection of deidentified data.

**RESULTS:** Subjects were African-American with an average age of 23.9 years, and average gestational age at delivery of 30.1 weeks. There were 10 (8.13%) intrauterine fetal deaths (IUFDs), and one neonatal death. Ascending amniotic fluid infection was noted in 50% and 92% meconium histocytes. All placentas had sickling in the intervillous space and the decidual vessels.

**CONCLUSIONS:** Sickling in the decidual vessels and poor placental perfusion may play a role in pregnancy loss in excess of what has previously been reported. A cohort control study appears to be in order.

**NARRATIVE:** Pregnant women with sickle cell trait are thought not to have increased maternal or fetal mortality/morbidity. Over a two year period, we studied 131 women with this hemoglobinopathy and found that 10.6% had intrauterine growth retardation (IUGR), 8.4% preterm premature rupture of the membranes, 8.1% intrauterine fetal demise (n = 10) at most occurring at 16 to 24 weeks, and one neonatal death. Amniotic fluid infection was noted in 50%, and meconium histocytes indicating intrauterine hypoxia were noted, as was unsuspected sickling in the placental vasculature. Based on this case series, sickle cell trait may not be as benign for the fetus as was previously thought.

### **Fertility and obstetrical complications in women with LMNA-related familial partial lipodystrophy.**

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**Objective:** Familial Partial Lipodystrophy due to LMNA (lamin A/C) mutations (FPLD2) is a rare disorder characterized by a selective loss of adipose tissue and insulin resistance. Dyslipidemia and severe diabetes often occur during its evolution. Only isolated and contradictory case reports have been published on the obstetrical prognosis in lipodystrophy. The aim of our study was to compare the fertility and occurrence of obstetrical complications of women with FPLD2 with those of non-affected relatives, women from the general population and women with polycystic ovary syndrome (PCOS).

**Material and methods:** Data was obtained from clinical follow-up of seven families with patients exhibiting mutations in LMNA (5 R482W, 1 R482Q, 1 R439C) (14 affected among 48 women).

**Results:** The mean number of live children per woman was 1.7 in affected patients vs. 2.8 in non-affected relatives. Fifty-four percent of LMNA-mutated women exhibited a clinical phenotype of PCOS, 28% suffered from infertility, 50% experienced at least one miscarriage, 36% developed gestational diabetes and 14% experienced eclampsia and fetal death. Mean blood leptin level was significantly lower in LMNA-mutated patients than in non-affected relatives (5.0+/-3.8 ng/ml vs 14.3+/-3.6;  $p < 0.001$ ) despite similar BMI (21.0+/-4.2 vs 22.4+/-2.2;  $p = 0.49$ ).

**Conclusion:** In these LMNA-linked lipodystrophic patients, the prevalence of PCOS, infertility and gestational diabetes was higher than in the general population. Moreover, the prevalence of gestational diabetes and miscarriages was higher in lipodystrophic LMNA-mutated women than previously reported in PCOS women with similar BMI. Women with lipodystrophies due to LMNA mutations are at high risk of infertility, gestational diabetes and obstetrical complications and require reinforced gynecological and obstetrical care.