ENDOGENOUS RISK FACTORS FOR CONGENITAL ANOMALIES: Smoking, Alcohol and maternal body mass idex

SMOKING

Neural tube defects

Although cigarette smoke is a well-established toxin and harmful to the developing embryo, the evidence for an independent effect on the occurrence of neural tube defects (NTDs) is mixed. In early studies the size of the study , potential confounding by social class and inadequate controls were often problems in interpretation of the data but no positive association between NTDs and smoking was been observed by Elwood et al., 1992 and Källén, 1998

Suarez 2011 examined the relation between NTDs and maternal exposures to cigarette smoke, including passive smoke exposure in a large case control multistate population-based National Birth Defects Prevention Study. A total of 1041 NTD cases and 5862 live birth controls, delivered during 1997 to 2004, were available for analyses. Compared with nonsmokers (and also not exposed to passive cigarette smoke), mothers exposed only to passive smoke had an increased NTD odds ratio (OR, 1.7; 95% confidence interval [CI], 1.4-2.0), adjusted for race-ethnicity, and study center. There was no increased OR for mothers who actively smoked 24 or fewer cigarettes per day. Mothers who smoked 25 or more cigarettes per day had an elevated OR (OR, 1.6; 95% CI, 0.9-3.0), but the OR adjusted for race-ethnicity, and center was compatible with the null.These results suggest that maternal exposure to passive smoke is associated with NTDs.

Limb defects

Early studies suggested a positive association with maternal smoking which did not reach statistical significance (Källén, 1997a). In a large case-control study in Hungary, the OR for total limb defects between categories of never, 1-9 cigarettes per day and 10 or more cigarettes per day was 1.68 (95% CI 1.26-2.24) adjusted for education and birth order (Czeizel et al., 1994). In a record linkage based study in Sweden, the OR of limb reduction defects associated with maternal smoking was 1.26 (95% CI 1.06- 1.50), adjusted for year of birth, maternal age and parity (Källén, 1997a). For the subset of infants bornin 1986 or 1991, additional adjustment for maternal socio-economic index was possible but had little impact on the OR observed, suggesting that the socio-economic status was not a major confounder. A dose-response relationship was apparent. In an analysis of birth defects in risk factor surveillance data from the northern Netherlands, in which combinations of 32 diagnostic categories and 77 risk factors recorded in a birth defects registry were analysed, a positive association between reduction deformities of the upper and lower limbs and maternal smoking was observed, with an OR of 1.73 (95% CI 1.04-2.78) (Cornel et al., 1997). This association was checked against data from the Atlanta area of the USA, and the corresponding OR was 1.31 (95% CI 0.92-1.84). In a study in California, an increased risk of limb reduction defects associated with maternal smoking was not observed in the absence of paternal smoking (Wasserman et al., 1996). In the study in the Netherlands already described, there was a positive association between maternal smoking and deformities of the foot (OR 1.73, 95% CI 1.27-2.34), which was supported by data from the Atlanta area (OR 1.26, 95% CI 1.04-1.52) (Cornel et al., 1997). In Washington State, the OR for club foot associated with maternal smoking was 2.6 (95% CI 1.6-4.0) for boys and 1.4 (95% CI 0.6-3.2) for girls (Alderman et al., 1991).

The relationship between maternal cigarette smoking during pregnancy and the risk of having a child with polydactyly, syndactyly, or adactyly was investigated by Man and Chang 2002. The records of 6,839,854 live births were examined to identify 5171 newborns with isolated polydactyly, syndactyly, or adactyly and 10,342 controls with no congenital anomalies. Maternal cigarette use during pregnancy was associated with a significantly elevated risk of having a child with a congenital digital anomaly (unadjusted odds ratio, 1.33; 95 percent confidence interval, 1.21 to 1.47; $p < 0.0001$). Univariate analysis indicated that maternal marital status

and maternal medical risk factors were potential confounding factors. After adjustment for these variables, the odds ratio remained significant (adjusted odds ratio, 1.31; 95 percent confidence interval, 1.18 to 1.45; $p < 0.0001$). Cigarette consumption per day was divided into four groups: no smoking, 1 to 10 cigarettes per day, 11 to 20 cigarettes per day, and 21 or more cigarettes per day. A statistically significant dose-response relationship was found when comparing each smoking category with the no-smoking reference group: 1.29 (95 percent confidence interval, 1.15 to 1.46), 1.38 (95 percent confidence interval, 1.12 to 1.71), and 1.78 (95 percent confidence interval, 0.97 to 3.26),respectively. Increased cigarette smoking during pregnancy resulted in an elevated risk of having a child with polydactyly, syndactyly, or adactyly.

Cardiac anomalies

Wasserman et al., 1996 found the association between maternal smoking and congenital cardiovascular anomalies to be inconsistent. In some analyses, the association with conotruncal heart defects specifically has been assessed, but again the results seem to be inconsistent. A study on Maternal smoking and congenital heart defects by Alverson et al 2011 observed statistically significant positive associations between self-reported first-trimester maternal cigarette consumption and the risk of secundum-type atrial septal defects (OR: 1.36 [95% confidence interval (CI):1.04-1.78]), right ventricular outflow tract defects (OR: 1.32 [95% CI:1.06-1.65]), pulmonary valve stenosis (OR: 1.35 [95% CI: 1.05-1.74]), truncus arteriosus (OR: 1.90 [95% CI: 1.04-3.45]), and levo-transposition of the great arteries (OR: 1.79 [95% CI: 1.04-3.10]). A suggestive association was observed for atrioventricular septal defects among infants without Down syndrome.

Parental cigarette smoking and the risk of congenital heart septal defects was studied by Kuciene and Dulskiene 2010. After adjustment for possible confounding factors - maternal education, social status, marital status - a statistically significant relationship was observed between parental smoking and congenital heart septal defects. Parental, maternal, and paternal smoking was significantly associated with a 2.27-fold (adjusted OR=2.27; 95% CI, 1.49-3.46), 2.2-fold (adjusted OR=2.20; 95% CI, 1.01-4.79), and 1.45-fold (adjusted OR=1.45; 95% CI, 1.03-2.03) increased risk of defects if compared with nonsmoking parents.

Gastroschisis

Gastroschisis (GS) continues to increase in frequency, with several studies now reported an incidence of between 4 and 5 per 10,000 live births. In early studies of maternal smoking and gastroschisis, a positive association was observed (Haddow et al., 1993; Torfs et al., 1994; Curry et al., 2000). In a combined analysis of three of the studies, the OR associated with maternal smoking was 1.6 (95% CI 1.2-2.2) (Haddow et al., 1993). In the study with the largest number of cases, the association with maternal smoking did not persist after adjustment for maternal education, annual family income, marital status, maternal recreational drug use, and factors associated with the mother's childhood (Torfs et al., 1994). Young maternal age would seem to be the main risk factor and the impact of several other putative risk factors, including smoking, may be less important than when first identified in early epidemiological studies (Holland et al 2010)

Orofacial clefts

Maternal smoking is a recognized risk factor for orofacial clefts. Maternal or fetal pharmacogenetic variants are plausible modulators of this risk. (Shi 2007)
A meta-analysis of the association between maternal cigarette smoking and oral clefts was carried out by (Wyszynski et al., 1997), based on 11 studies. These authors reported combined ORs for both cleft lip and cleft palate of about 1.3, based on 11 studies. In addition, an increased risk of similar magnitude has been observed in more recent studies (Shaw et al., Lorente et al.)

Hypospadias

In a large study in Sweden, maternal smoking was not associated with an increased risk of hypospadias (Akre et al., 1999), but Brouwers et al 2007 in a study evaluating a wide spectrum of potential risk factors for hypospadias found maternal smoking during the 3 months immediately prior to conception or in the first trimester of pregnancy also appeared to increase the risk of hypospadias (OR=1.5; 95%CI: 1.0-2.4), They concluded that that genetic predisposition, placental insufficiency, and substances that interfere with natural hormones play a role in the etiology of hypospadias.

Down syndrome

The results of studies of the association between maternal smoking and Down Syndrome are inconsistent (Little & Vainio, 1994; Chen et al., 1999). A number of earlier studies, mostly based on small numbers of infants, reported an inverse association with smoking (Källén, 1997c; Chen et al., 1999). In a metaanalysis published in 1993, a combined OR of 0.84 (95% CI 0.71-0.99) was calculated (Kline et al., 1993). The authors noted that publication bias was a potential explanation for this observation. In recent large studies in Sweden, Washington State and California, no overall association between Down Syndrome overall and smoking was observed (Källén, 1997c; Chen et al., 1999; Torfs & Christianson, 2000). In the study in Washington State, an inverse association was apparent when broad categories of maternal age were adjusted for, but no association was apparent when exact year of maternal age in conjunction with ethnic group and parity were adjusted for (Chen et al., 1999). This suggests that there was substantial potential for residual confounding by maternal age in studies of maternal smoking and Down Syndrome.

Rudnicka et al 2002 investigated the Influence of maternal smoking on the birth prevalence of Down syndrome and on second trimester screening performance and concluded there is no evidence of an association between the birth prevalence of Down syndrome and maternal smoking. .

Maternal obesity

Obesity is defined as a condition of excess body fat and is associated with a large number of debilitating and life threatening disorders. As the direct measurement of body fat is difficult Body Mass Index (BMI) is typically used to classify overweight and obese adults. The World Health Organisation (WHO) has recently published international standards with obesity defined as a BMI > or = to 30kg/m2 . Methods of determining maternal body composition in pregnancy and its relevance to perinatal outcome have been investigated (McCarthy 2004) but these methods remain cumbersome and impractical.

Few recent studies have examined the relation between maternal prepregnancy obesity and overweight in a range of congenital anomalies. Watkins et al. 2003 in a population-based case-control study of several selected major birth defects, using data from the Atlanta Birth Defects Risk Factor Surveillance Study, compared the risks for obese women (BMI > or =30) and overweight women (BMI 25.0-29.9) with those for average-weight women (BMI 18.5-24.9). Obese women were more likely than average-weight women to have an infant with spina bifida (unadjusted odds ratio [OR]: 3.5; 95% confidence interval [CI]: 1.2-10.3), omphalocele (OR: 3.3; 95% CI: 1.0-10.3), heart defects (OR: 2.0; 95% CI: 1.2-3.4), and multiple anomalies (OR: 2.0; 95% CI: 1.0-3.8). Overweight women were more likely than average-weight women to have infants with heart defects (OR: 2.0; 95% CI: 1.2-3.1) and multiple anomalies (OR: 1.9; 95% CI: 1.1-3.4) This study confirmed the previously established association between spina bifida and prepregnancy maternal obesity and found an association for omphalocele, heart defects, and multiple anomalies among infants of obese women. An association between heart defects and multiple anomalies and being overweight before pregnancy was also found.

Cardiovascular defects (CVD)

A prospective case-control study by Cedergren and Kallen 2003 examined whether obese women have an increased risk of CVD in their offspring compared with average weight women. Information was obtained from Swedish medical health registers. Obesity was defined as BMI >29 kg/m_2 and morbid obesity was defined as BMI >35 kg/m_2 . In comparison with average weight women (BMI = 19.8 to 26 kg/m_2. the obese mothers had an increased risk for CVD compared with the average weight mothers [adjusted odds ratio (OR) = 1.18; 95% CI, 1.09 to 1.27], which was slightly higher for severe CVD (adjusted OR = 1.23; 95% CI, 1.05 to 1.44). With morbid obesity, the OR for CVD was 1.40 (95% CI, 1.22 to 1.64), and for severe CVD the OR was 1.69 (95% CI, 1.27 to 2.26). There was an increased risk for all specific defects studied among the obese women, but only ventricular septal defects and atrial septal defects reached statistical significance. The authors suggest undetected type 2 diabetes in early pregnancy as a possible explanation.

Neural tube defects and glycemic control

It has been reported that maternal diabetes, prepregnancy obesity, hyperinsulinemia, and intakes of sweets to be associated with increased risks of neural tube defects (NTDs) (Shaw et al 2003). The interdependence of these factors suggests a common pathogenesis via altered glycemic control and insulin demand. Maternal periconceptional dietary intakes of sucrose,glucose, fructose, and foods with higher glycemic index values were examined for their influence on the risk of having NTD-affected pregnancies by Shaw et al 2003. In this population-based case-control study in California the risk of having an NTD-affected pregnancy was not substantially elevated in relation to periconceptional intakes of glucose or fructose. A 2 fold risk was observed for higher intakes of sucrose and foods with higher glycemic index values. Elevated risks were observed for high sucrose intake. For higher glycemic index values, adjusted elevated risks of > or = 4-fold were observed in women whose body mass index (in kg/m(2)) was > 29. This supports observations that potential problems in glucose control are associated with NTD risk even among nondiabetic women. Shaw et al in 2000 investigated whether finer phenotypic classifications of spina bifida, in combination with other factors, were associated with a BMI of >29 kg/m_2. Data were derived from a case-control study of fetuses and infants with NTDs among California births. Women with a BMI of >29 kg/m_2 compared with those </=29 kg/m_2 revealed an odds ratio (OR) of 2.2 [95% CI] = 1.4-3. 3) for spina bifida in their infants and fetuses. Elevated risks were observed for each spina bifida subphenotype, and risks varied by subphenotype: open spina bifida, OR = 2.0 (1.2-3.1); closed (skin-covered), 3.3 (1.4-7.5); isolated, 2.2 (1.4-3.4); nonisolated, 1.9 (0.9-4.2); high, 4.5 (2.1-9.6); low, 1.9 (1.2-2.9); open/isolated/high, 7.1 (2.8-18.1); and open/isolated/low, 1.8 (1. 1-3.1). Risks were higher among female infants/fetuses and foreign-born Latinas, and for some phenotypes the risks were quite large, e.g., OR = 8.3 (2.9-23.6) for "closed" spina bifida among female infants/fetuses whose mothers were >29 kg/m_2 compared with males whose mothers were </=29 kg/m(2). Maternal periconceptional vitamin use was not observed to influence risk as greatly across phenotypes. The observed pathogenetic heterogeneity of prepregnant obesity and spina bifida risks suggests that there are likely to be several biologic mechanisms underlying the association.

Maternal obesity and congenital anomalies in Europe

Few European studies are reported on maternal obesity and congenital anomalies.Queisser-Luft 1998 et al investigated the risk of congenital malformations for newborn of obese women (BMI > or = 30) compared with women of average prepregnancy weight in a prospective, population-based case-control study of 20,248 newborn born in the city of Mainz. The prevalence of malformations in children of obese mothers was 11.1% approximately 4% higher than those of the total study population. There is a significant odds ratio for major malformations (OR 1.3; KI 1.0-1.7). Statistically significant associations were calculated for malformations of the internal urogenital system (OR 1.7; 1.1-2.8), the eyes (OR 5.0; 1.3-20.0) and for orofacial clefts (OR 1.7;1.1-2.8). Among the specific malformations the highest associations occurred for encephalocele (OR 7.3; 1.1-50.6), common truncus arteriosus (OR 6.3; 1.6-24.8) and Potter sequence (OR 6.3; 1.6-24.8). Adjustment for confounding factors (e.g.maternal diabetes mellitus and age) did not change the odds ratios malformations.

Increasing BMI, increasing risk of congenital anomaly – underweight decreases risk

In Atlanta Watkins et al 1996 investigated whether the risk of having an infant with anencephaly or spina bifida is greater among obese women than among average-weight women.. After adjusting for other variables they found that, compared with average-weight women, obese women (BMI> 29) had almost twice the risk of having an infant with spina bifida or anencephaly (odds ratio = 1.9;95% confidence limits = 1.1, 3.4). A woman's risk increased with her BMI: adjusted odds ratios ranged from 0.6 (95% confidence limits = 0.3, 2.1) for very underweight women to 1.9 for obese women.

ALCOHOL

Alcohol is a potent teratogen in humans, and prenatal alcohol exposure is a leading preventable cause of birth defects and developmental disabilities (Krulewitch 2005). Fetal alcohol syndrome (FAS) refers to a pattern of birth defects found in children of mothers who drank during pregnancy. FAS has four criteria: maternal drinking during pregnancy, a characteristic pattern of facial abnormalities,growth retardation, and brain damage (often manifested by intellectual difficulties or behavioral problems). As surveillance and research have progressed, it has become clear that FAS is but a rare example of a wide array of defects that can occur from exposure to alcohol in utero. At least 1 in 10 women will continue to consume alcohol during pregnancy, putting their fetuses at risk for the effects of alcohol exposure.

Warren and Bast as early as 1988 suggested that FAS outranked Down's syndrome and spina bifida in prevalence and presented the leading known cause of mental retardation. Because a safe limit of alcohol consumption in pregnancy is not defined, abstinence during pregnancy is the most prudent preventive measure. Factors such as race, beer drinking, maternal weight gain, and low socioeconomic status are associated with a statistical increase in the incidence of FAS. In families where one child has been diagnosed as having FAS, the incidence rate can be as much as 405-fold higher than the worldwide average. Neurobehavioral deficits can occur in the offspring of drinking mothers in the absence of a diagnosis of full FAS. The deficits differ with age and seem to persist into adulthood. Mental retardation or borderline mental retardation is a nearly ubiquitous neurological deficit in diagnosed FAS. In one study, it occurred in 75 percent of the non-FAS offspring of mothers who continued to drink heavily throughout their pregnancy.From the mid-1970s, having established that alcohol is a teratogen, scientists have been trying to uncover the mechanism by which alcohol exerts its embryotoxic effects. Recent promising neuroanatomical studies have demonstrated that alcohol has a deleterious effect on neuronal migration and hence on the development of the cerebral cortex. Other studies have shown that prenatal alcohol exposure,by adversely affecting hippocampal development,may be responsible for the learning deficits so frequently encountered in FAS children. Other research has implicated prostaglandins in the mechanism of alcohol-related dysmorphology.

Orofacial clefts

DeRoo et al 2008 examined the association between maternal alcohol consumption and oral clefts in Norway. Compared with nondrinkers, women who reported binge-level drinking (>or=5 drinks per sitting) were more likely to have an infant with cleft lip with or without cleft palate (odds ratio = 2.2, 95% confidence interval: 1.1, 4.2) and cleft palate only (odds ratio = 2.6, 95% confidence interval: 1.2, 5.6). Odds ratios were higher among women who binged on three or more occasions: odds ratio = 3.2 for cleft lip with or without cleft palate (95% confidence interval: 1.0, 10.2) and odds ratio = 3.0 for cleft palate only (95% confidence interval: 0.7, 13.0). Maternal binge-level drinking may increase the risk of infant clefts but in contrast Meyer et al 2003 found low maternal alcohol consumption during pregnancy was not associated with oral clefts .

Cardiac defects

In Spain, a case-control study by Martinez-Frias et al. reported that higher risk of developing CHDs was in the group with the highest-level prenatal exposure to alcohol.

Neural tube defects

(see combined factors below)

COMBINED FACTORS

Grewal et al investigated maternal periconceptional smoking together with alcohol consumption and risk for select congenital anomalies. The study examined the association between maternal smoking and alcohol use (including binge drinking) during the periconceptional period and the risk of orofacial clefts, NTDs, and conotruncal heart defects in offspring. Maternal smoking of five cigarettes or less per day was associated with reduced risks of NTDs (OR 0.7; 95% CI: 0.3, 1.4), whereas the risk associated with higher cigarette consumption was lower for conotruncal heart defects (OR 0.5; 95% CI: 0.2, 1.2). Maternal intake of alcohol less than 1 day per week wasassociated with a 1.6- to 2.1-fold higher risk of NTDs (95% CI: 0.9, 2.6),d-transposition of the great arteries (95% CI: 1.1, 3.2), and multiple cleft lip with or without cleft palate (CLP) (95% CI: 0.8, 4.5). Risks associated with more frequent alcohol intake were 2.1 for NTDs (95% CI: 1.1, 4.0) and 2.6 for multiple CLP (95% CI: 1.1, 6.1).

Maternal smoking, body mass index, and neural tube defects were studied by Källén 1998 Among 1,199,701 infants born in 1983-1993 with known smoking exposure in early pregnancy, 621 infants with NTDs were selected. After ontrolling for year of birth, maternal age, parity, education level, BMI, and immigrant status (yes/no), a highly significant, protective effect of maternal smoking on the incidence of NTDs was found. The adjusted odds ratios (OR) and(95% confidence intervals (CI)) for maternal smoking among infants with NTDs(total), anencephaly, and spina bifida were 0.75 (0.61-0.91), 0.49 (0.28-0.85),and 0.76 (0.61-0.95), respectively. A protective dose-response effect of smoking was indicated but was not statistically significant. The association between NTDs and maternal BMI found in earlier studies was supported. Women with BMI >26.0 were found to be at higher risk of having an infant with NTD compared with women in other BMI classes (adjusted OR=1.35, 95% CI 1.00-1.83). For women with BMI > or =29, the corresponding odds ratio was 1.29 (0.81-2.05). No obvious explanation was found, either for the detected association between NTDs and BMI, or for the protective effect of maternal smoking.

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