Maternal obesity and risk of congenital anomalies.

Summary

Obesity is increasing at an alarming rate. Body Mass Index (BMI) is typically used to classify overweight and obese adults. Maternal obesity is associated with an increased risk for congenital anomalies. Obese women were more likely to have an infant with spina bifida, omphalocele, heart defects and multiple anomalies . Overweight women were more likely to have infants with heart defects and multiple anomalies. Maternal obesity often leads to diabetes which is itself associated with increased risk of birth defects . Potential problems in glucose control are associated with NTD risk even among nondiabetic women. Whilst increasing BMI implies increasing risk of congenital anomaly being underweight in some cases decreases risk. Maternal obesity may cause difficulty in prenatal diagnosis by ultrasound and maternal serum alfa-protein. Consanguinity may exacerbate risk of congenital anomalies in obese mothers. Whilst obesity in the offspring is not classed as a congenital anomaly it is an adverse outcome on which to reflect.

INTRODUCTION

Obesity: definition, prevalence and measurement

Obesity is increasing at an alarming rate worldwide making it an important individual and public health issue. The prevalence of obesity has doubled or even trebled in less than two decades, while in children this is rising at an even faster rate in some regions of Europe to levels of up to 36% in parts of Italy and else where. (James et al. 2004). Obesity is defined as a condition of excess body fat and is associated with a large number of debilitating and life threatening disorders. Mortality and morbidity due to obesity are linked to the distribution of body fat, with the highest risk linked to excessive abdominal fat (central obesity). Central obesity is linked to a number of diseases such as cardiovascular disease and non-insulin dependent diabetes mellitus (NIDDM). Different populations (e.g. Asians) have differing levels of central obesity. In India 20% of adults who were not overweight or obese still had central obesity and greater risk of developing these diseases. (Gopalan 1998). 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/m^2 . Prior to this obesity and overweight classification varied leading to difficulty in understanding population prevalence and results of scientific studies. Obesity can be further classified by its severity. BMI provides a simple, convenient index but with certain limits. 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.

Maternal obesity: risks in pregnancy

Maternal obesity adversely impacts pregnancy outcome primarily through increased rates of hypertensive disease (chronic hypertension and pre-eclampsia), diabetes (pregestational and gestational), cesarean section and infections Castro & Avina 2002. It is associated with a higher rate of venous thromboembolic disease and respiratory complications, fetal mortality and preterm delivery. Maternal obesity also increases the risk of delivering a large for gestational age or macrosomic neonate, who is in turn at an increased risk of

subsequent childhood obesity and its associated morbidity. Maternal obesity is associated with an increased risk for congenital anomalies. Maternal obesity often leads to diabetes which is itself associated with increased risk of birth defects. **Simmons and Breir 2002** proposed fuel mediated teratogenesis, exposing the fetus to an excess of fuel (eg.glucose) causes fetal changes leading to malformations.

Maternal obesity and congenital anomalies

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.

NTD risk by phenotype and sex

Shaw GM, Todoroff K, Finnell RH, Lammer EJ.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.

Maternal obesity and prenatal diagnosis – ultrasound and maternal serum alfa-protein

Difficulty in ultrasound diagnosis has been reported by several authors **(Ozcutlu 1999, Rane 1990, Buskens et al 1996)** . A study by **Wong et al 2003** reports of 130 scans performed 48 (37%) were sub-optimal due to maternal obesity. Hence whilst maternal obesity represents a higher risk factor for congenital anomalies the probability of a prenatal diagnosis is lower. This needs to be taken into account in the interpretation of prevalence data as live births may be higher to obese mother due to lack of prenatal diagnosis and terminations. **Drugan et al 1989** analysed the effect of a previously published linear correction formula for weight on the frequency of abnormal maternal serum alpha-fetoprotein MSAFP results. Correction for maternal weight compensates for the dilution effect of a larger plasma volume in women of greater weight. Without correction, the highest rate (15%) of low MSAFP results was obtained in the obese population. Conversely, the rate of elevated MSAFP was highest (3.8%) in the lowest maternal weight group. Correction for weight up to 250 lb significantly increased the rate of abnormally high results in the obese group, indicating an overcorrection effect. The authors recommend results in women weighing more than 200lbs should be corrected as if the weight were 200 lbsonly.

Consanguinity

Van Allen and Myhre DATE reported a term stillborn female infant with multiple congenital anomalies (MCA) which had not previously been reported as occurring together born to parents who are first cousins. There was a strong maternal family history of adult-onset diabetes. Structural defects were similar to those in 2 sibs born to a prediabetic mother with a first cousin marriage as well as in focal dermal hypoplasia. The authors conclude that parental consanguinity is suggestive of an autosomal recessive disorder or alternatively, it may represent a combined multifactorial effect making the conceptus more sensitive to metabolic teratogens and thus placing it at increased risk for disruption of normal development.

Obesity breeds obesity

It has been hypothesised that increasing maternal obesity is associated with increasing maternal glycaemia stimulating fetal insulin secretion and raising the potential for obesity in the offspring (**Simmons and Breier 2002)**. Mothers also tend to pass their eating habits to their children (**Cundy 2002)** Whilst obesity in the offspring is not classed as a congenital anomaly it is an adverse outcome on which to reflect.

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Oct 2004

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