OBSTETRICS

Association between maternal body mass index and congenital heart defects in offspring: a systematic review

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The aim of this study was to investigate the relationship between maternal body mass index and all congenital heart defects (CHDs) combined and 11 individual defects. PubMed, ELSEVIER ScienceDirect, and Springer Link (up to February 2013) were searched, and the reference list of retrieved articles was reviewed. Three authors independently extracted the data. The systematic review included 24 studies, 14 of which were included in a metaanalysis. Statistical software was used to perform all statistical analyses. Fixed-effects or random-effects model was used to pool the results of individual study (expressed as odds ratios [ORs] with 95% confidence intervals [CIs]). A dose-response effect was observed between overweight, moderate obesity, and severe obesity and a pregnancy with any CHD (the pooled ORs: OR, 1.08 [95% CI, 1.02—1.15]; OR, 1.15 [95% CI, 1.11—1.20]; and OR, 1.39 [95% CI, 1.31—1.47], respectively) as well as some individual defects such as hypoplastic left heart syndrome, pulmonary valve stenosis, and outflow tract defects. When we excluded mothers with diabetes mellitus, the pooled ORs for all CHDs combined were 1.12 (95% CI, 1.04—1.20) and 1.38 (95% CI, 1.20—1.59) for moderately obese and severely obese, respectively. The highest increased risk was severely obese mothers for tetralogy of Fallot (OR, 1.94; 95% CI, 1.49—2.51). Being underweight did not increase the risk of any of the aforementioned CHDs but did increase the risk of aortic valve stenosis (OR, 1.47; 95% CI, 1.01—2.15]). The results of our study showed that increasing maternal body mass index was associated with an increasing risk of CHDs; severe obesity was an even greater risk factor for the development of CHDs.

Key words: body mass index, congenital heart defect, metaanalysis, obese, systematic review

Obesity among the general population has increased dramatically over the past decades, especially in the western world and in urbanized developing countries, and represents a worldwide public health concern.[1,2] Even more compelling is the increasing prevalence of obesity among reproductive-aged women. Epidemiologic data from the National Health and Nutrition Examination Survey described that, from 2007-2008, 28-32% of childbearing-aged women were obese and that 7.2-8.4% of them were morbidly obese (body mass index [BMI], $\geq$40 kg/m^2).[3] From a public health perspective, recent studies have highlighted the increased risks that are associated with obesity in pregnancy and have appealed for optimal treatment of the pregravid obese women. Numerous studies have shown that obese women appear to be at a higher risk of pregnancy complications, such as preeclampsia,[4,5] gestational diabetes mellitus,[4,6] preterm delivery,[6] and cesarean delivery,[5-7] as well as adverse fetal and neonatal outcomes, such as congenital heart defects (CHDs),[8,9] neural tube defects,[8,10] and orofacial clefts.[11]

Among the aforementioned birth defects, CHD is a serious medical problem. The reported prevalence of CHDs among live births ranges from 0.4—1.0%, with regional variations.[12-16] Approximately 25,000-35,000 infants in the United States are affected by CHDs each year.[17] CHDs are among the most common birth defects and accounts for nearly one-third of all major congenital anomalies,[18] substantially contributing to death during infancy and childhood, especially in the first year of life.[19,20] But, the exact cause of CHDs is largely unknown. Studies have suggested that overweight/obesity is likely a major contributor to the increased incidence of CHDs. However, because of the limitations of sample size and epidemiologic study methods (ie, the lack of large birth cohort studies), the findings have been inconsistent. To assess and quantify the association between maternal BMI and the risk of a pregnancy with CHD, we conducted the systematic review and metaanalysis, using the currently available observational studies.

Materials and methods

Literature search and selection of studies

We carried out a comprehensive computerized search of Pubmed (January 1953 to February 2013), ELSEVIER ScienceDirect (SDOS; January 1953 to February 2013), and Springer Link (1996 to February 2013) using the search strategy: "(birth defects OR congenital malformations OR CHDs) AND (underweight OR overweight OR high weight OR obes* OR BMI OR maternal weight) AND (*pregnancy)". Additional articles were identified by reviewing reference lists of articles. All searches were restricted to existing English-language articles.

Potentially eligible articles were identified according to the following inclusion criteria: (1) original epidemiologic

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studies only; (2) participants were pregnant women; (3) a measured or estimated prepregnancy or early pregnancy weight was reported; and (4) the outcome was pregnancies with all CHDs combined or any specific defect. Studies included in the metaanalysis were (1) reported BMI category in the standard format (kilograms per square meter), (2) reported odds ratios (ORs) accompanying 95% confidence intervals (CIs) or had sufficient raw data to calculate, and (3) had a reference group of normal-weight, no inclusion of underweight in the reference category. In the case of multiple publications that resulted from the same data, only the study that contained the most comprehensive information or the most recent study was selected. Disagreements regarding criteria fulfillment were resolved by discussion among the 3 researchers.

Data extraction and outcomes

Two reviewers (C.G. and S.X.) first screened studies by title/abstract and made exclusions based on the original eligibility criteria. Studies that met the inclusion criteria were reviewed independently by 3 authors (G.C, X.S. and L.Z.) using a piloted data extraction form. The retrieved information included study characteristics (ie, first author, publication year, study period, location, study design), participant information (ie, whether mothers had preexisting diabetes mellitus [PDM] or gestational diabetes mellitus [GDM]), sources and categorizations of maternal BMI/weight, sources and ascertainment of cases, and confounder-adjusted or unadjusted ORs and 95% CIs. Discrepancies among the 3 reviewers were resolved by discussion.

We conducted metaanalyses for all CHDs combined and 11 specific defects on the condition that there were at least 2 studies with available data. The 11 individual defects were atrial septal defect (ASD), aortic valve stenosis (AVS), atrioventricular septal defect (AVSD), conotruncal defects (CD), coarctation of the aorta (COA), hypoplastic left heart syndrome (HLHS), outflow tract defects (OTD), pulmonary valve stenosis (PVS), transposition of the great arteries (TGA), tetralogy of Fallot (TOF), and ventricular septal defect (VSD).

Statistical analysis

Different thresholds for categorizing maternal BMI have been used in different studies, making it difficult to compare risk estimates. In the meta-analysis, we categorized maternal BMI into 5 levels that are most consistent with the World Health Organization guidelines[21] and are used most commonly in studies. Women with a BMI of 18.5-24.9 kg/m^2 were defined as normal weight (reference group): underweight, $<$18.5 kg/m^2; overweight, 25.0-29.9 kg/m^2; moderately obese, 30.1-34.9 or 30.1-39.9 kg/m^2; and severely obese, $\geq$35.0 or $\geq$40.0 kg/m^2 (either-or, consistent with the original studies). The latter 2 categories were combined in a group of 'obese' ($\geq$30.0 kg/m^2; Table 1).

The metaanalysis was conducted and reported according to the Statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[22] We extracted data from each study and analyzed with the data with RevMan software (version 5.2; Cochrane Review Manager; Cochrane Collaboration, Oxford, UK). Although several of the original studies presented adjusted ORs, the adjustment for potential confounding factors varied among studies, and no summary adjusted ORs could be calculated. Moreover, the crude and adjusted estimates in original studies were mostly similar. Therefore, we used only crude estimates in the metaanalysis.

Weight for each study (for dichotomous outcomes this weight was based on the size of the study and the number of events) was calculated to determine how much each individual study contributed to the pooled estimate. Heterogeneity was estimated by the chi-square test (considered to be an evidence of significant heterogeneity if $P < .1$) and the Cochrane Q test (quantified with the I^2 metric, which described the total variation in OR attributable to heterogeneity).[23] $I^2 = 0$ indicates no heterogeneity; the larger value indicates the greater heterogeneity. As is typical in meta-analyses, I^2 also was used to select the most appropriate pooling method[24]: fixed-effects models were used for $I^2 \leq 50\%$, and random-effects models were used for $I^2 > 50\%$. Z-test was applied for testing the overall effect; a probability value of $< .05$ was considered statistically significant. Forest plots were constructed to present study-specific pooled ORs and 95% CIs graphically. The presence of publication bias was tested with the use of a combination of Egger's regression asymmetry test and Begg's rank correlation test (using Stata software, version 11.0; StataCorp, College Station, TX).

Sensitivity analyses were performed to test the robustness of the overall findings for CHDs as a group: (1) fixed-effect models vs random-effect models; (2) cases ascertained among live births, stillbirths, and terminations vs live births and stillbirths vs only live-born infants or newborn infants; (3) $<$500 cases vs $\geq$500 cases; (4) excluded PDM but included GDM vs excluded both conditions; and (4) studies conducted in the United States vs in other countries (Table 2).

Results

Study identification and selection

As shown in Figure 1, the primary search of Pubmed, SDOS, and Springer Link identified 5929 articles, 5863 of which were excluded based on the review of the title/abstract; further review of the reference lists of the 66 articles identified another 13 studies for possible inclusion. By reviewing the whole 79 articles according to the prespecified inclusion criteria, 56 articles were excluded. Therefore, 23 articles (which contained 24 eligible studies) were screened for final inclusion in the systematic review. As Table 1 shows, among the 24 studies, 18 (75%) were case-control studies, and 6 (25%) were cohort studies; 12 studies (50%) were conducted in the United States; 6 studies (25%) were conducted in Sweden, and the remaining 25% of studies were from another 5 countries; 7 studies were conducted for the primary purpose of investigating the association between maternal BMI and CHDs; and the remaining studies reported data regarding this relationship as a secondary aim.