Original Article

Relation between Maternal Obesity and Fetal Congenital Malformations

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Abstract

Background: There is evidence suggests that there is an association between maternal obesity and some congenital abnormalities. **Objective:** Since there is no local study has been examined the relation between maternal pregnancy obesity and overweight and fetal congenital malformations, we explored this relation in Babylon women and compared our findings with previous studies. **Materials and Methods:** This prospective study was carried on patients admitted to Babil Obestetric and Pediatric Teaching Hospital in Babylon city, Iraq, from April 2016 to April 2017. Data were collected by history, clinical examination, and investigations and body mass index was measured for all patients. All neonates examined by pediatrician and surgeon to detect any congenital malformations. All the mothers of case infants or control infants of age more than 35 years or <18 years were excluded from this study. Control infants are infants without any congenital malformations. All the mothers with positive tests for toxoplasmosis, cytomegalovirus, rubella, or proved to have diabetes and surgical problems were also excluded from the study. All the mothers living in an area known to have a history of radiation exposure were also excluded. The affected infants have been identified. The risks for obese and overweight women were compared with those for average-weight women. **Results:** Obese women (study cases) have more infants with neural tube defect, especially spina bifida and anencephaly than were average-weight women (control). Obese women were more likely to have an infant with hydrocephaly defect in compare to average-weight women. Over-weight women also have an infant with defects, such as meningocele, spina bifida, meningocele and hydrocephaly, multiple abnormalities, hydrocephaly, meningocele and anencephaly, and anencephaly. There were no significant associations between congenital malformations and underweight women. **Conclusions:** Our study gives an evidence that there is an association between maternal obesity and fetal congenital malformations. Maternal obesity constitutes a serious health risk for the fetus the impact of which increases with the degree of obesity.

Keywords: Anencephaly, birth defect, fetal congenital malformation, maternal obesity

Introduction

The World Health Organization considers obesity as one of the most serious global health problems of the 21st century.[1] Regarding obesity during pregnancy, the recommended gestational weight gain is 11.5–16.0 kg (0.5-2.0kg for the first trimester and 0.35-0.50kg per week for the second and third trimester).[2] It is strictly recommended for overweight and obese pregnant women to limit weight gain to a minimum and this aim is achieved by a balanced diet of high nutritional value, which results in both weight control and normal embryo growth. Although excess body weight has been correlated with increased risk for first-trimester miscarriage, the results of various studies are controversial and far from being conclusive.[3]

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Quick Response Code:

Website: www.medjbabylon.org

DOI: 10.4103/MJBL.MJBL_13_20

Pregnancy *per se* constitutes a prothrombotic state characterized by an increase in the plasma concentration of coagulation factors, VII, VIII, and X, a decrease in protein S and inhibition of fibrinolysis.[4] These changes in combination with other risk factors, such as advanced maternal age, high parity, cesarean section, preeclampsia, and obesity, result in an increased risk

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Submitted: 06-Mar-2020 **Accepted:** 03-Jun-2020
Published Online: 16-Sep-2020

How to cite this article: Dawood IS, Jupori SA. Relation between maternal obesity and fetal congenital malformations. Med J Babylon 2020;17:257-61.

for venous thrombosis; body mass index (BMI) >25 kg/m^2 combined with oral contraceptive pills greatly increases the risk of thrombosis among women aged 15–45 years.[5]

Approximately 3%–10% of women will be affected by gestational diabetes.[6] Despite many factors contribute to this, such as ethnic origin, age, and family history, obesity constitutes an independent risk factor as the incidence of gestational diabetes is two- to threefold higher in obese and overweight as compared to normal-weight women.[6] Moreover, obesity and diabetes play independent roles in determining fetal size. Women with gestational diabetes and normal body weight who control their glycemia with diet, insulin, or antidiabetic drugs present an incidence of neonatal macrosomia comparable to that of women without diabetes.[7] In addition, insulin treatment prevented macrosomia in overweight and obese women.

During pregnancy, obese women face increased risk of developing hypertension, preeclampsia, and gestational diabetes. Specifically, women with a BMI >30 kg/m^2 have a two- to threefold higher risk for developing preeclampsia, while this risk doubles for an increase in BMI prior to pregnancy by 5–7 kg/m^2.[8] Waist circumference is considered as the most sensitive index of visceral obesity, which is directly associated with an increased risk for hypertensive disorders.

On the other hand, obesity and a previous pregnancy complicated by preeclampsia constitute the main risk factors for developing severe preeclampsia in the current pregnancy. Preeclampsia is also associated with an increased risk for coronary heart disease in later life.[9]

Current evidence indicates that obesity during pregnancy leads to induced preterm delivery but not spontaneous preterm birth, which is usually encountered in women with low BMI.[10] Nevertheless, the data are still inconclusive.[11]

Several studies suggest a twofold[6] increase in the risk for cesarean section in obese women even without additional risk factors. Cesarean section in this group is of great concern, as women who are overweight or obese are more susceptible to postoperative complications, such as excessive blood loss, deep venous thrombosis, wound infection, and postpartum uterine infection.[12]

Obesity-related adverse outcomes in labor included prolonged labor and failure to progress, increased rate of cesarean sections, and shoulder macrosomia and dystocia, while postpartum complications of obesity included postpartum hemorrhage and lactate dysfunction.

Obesity is associated with an increased risk of failure to initiate lactation and decreased duration of lactation. Maternal obesity is implicated in altering metabolism, the hypothalamic–pituitary–gonadal axis, and fat.

The most common complications of maternal obesity for the fetus are intrauterine death, genetic disorders, and macrosomia. In the long term, large for gestational age (LGA) neonates of obese or diabetic mothers are prone to the development of childhood obesity and metabolic syndrome in their adult life.[13] Obesity is also associated with congenital anomalies of the fetus.[14]

Maternal overweight and insulin resistance before pregnancy effect fetal growth, as is reflected in the birth weight.[15]

Obesity and insulin resistance alter placental function which, during the last weeks of pregnancy, increases the availability of glucose, free fatty acids, and amino acids to the fetus.[16] Thus, maternal hyperglycemia induces fetal hyperglycemia and as a consequence, hypertrophy/hyperplasia of the fetal pancreas and hyperinsulinemia. Insulin has a direct effect on cell division that leads to macrosomia. Therefore, women with diabetes are at high risk of delivering macrosomic babies. There seems to be a quantitative relationship between maternal BMI and the risk of delivering a macrosomic/LGA neonate.[17] Macrosomia, as well as maternal height and weight, gestational age, and the number of prior deliveries, is considered a reliable predictor of the risk of obstetrical events, such as shoulder dystocia and injury of the branchial plexus.[6]

The abnormal development of the fetus results in increased morbidity during childhood, adolescence, and adulthood, a phenomenon known as "fetal programming" or "developmental origin of adult disease."[18] The fetal adjustment to the uterine environment leads to permanent changes in the phenotype (i.e., physical structure, physiology, and metabolism) which might not be fully functional in extrauterine conditions. To explain this phenomenon, particularly the connection between fetal development and Type 2 diabetes, the hypothesis of the "thrifty phenotype" was formulated. According to this, poor nutrition during intrauterine life, as reflected in low birth weight, results in adverse physiological or morphological characteristics ("developmental plasticity") in certain organs (e.g., pancreas), while it respects others (e.g., brain). In addition to Type 2 diabetes, the "thrifty phenotype" hypothesis possibly accounts for such diseases as hypertension, hyperlipidemia, atherosclerosis, cardiovascular disease, and stroke, their common denominator being insulin resistance.[19]

Materials and Methods

Our study is a prospective study and uses active case finding among records of birth in Babil Obstetric, Pediatric Teaching Hospital, Babylon province, Iraq. Affecteds infants that have been identified are (live birth, still birth, preterm labor and abortion more than 20 weeks of gestation). To be eligible for inclusion as either a case infant or a control infant had to be born between April 2016 and April 2017. The control are infants without any congenital abnormalities.

We collected sixty mothers as control and sixty mothers for the case. All the mothers of case infants and control infants completed an interview with questions on age maternal health, medication use, pregnancy history and fertility, demographics, family history, nutrition, occupational and environmental exposures, and tobacco use. Mother's weight and height also had been recorded for the calculation of BMI. BMI is defined

as weight in kilograms divided by the square of the height in meters. Patients are considered obese if BMI average between (30.0- and 34.9). If BMI between (25 and 29.9), patients considered overweight. If BMI between (18.5 and 24.9), patients considered as normal weight while if BMI was below (18.5), patients considered underweight.

All the mothers living in an area known to have a history of radiation exposure were excluded. Furthermore we completed with her full investigations: Blood was checked for sugar (to excluded the possibility of diabetes (fasting and random). Test for Toxoplasmosis was done using immunoglobulin (IgM)/Plasmatec Lab Product Ltd.,/UK, and IgM/creatine phosphokinase/USA, on site rabbit test cassette. Cytomegalovirus IgM Ag coated plate (Ziploc/Spain) and Rubella IgM (Bio kit/French), were also done. To exclude the possibility of perinatal infection, All the mothers of age <18 years or more than 35 years were excluded.

The fetus or the neonate was examined by a pediatrician to catch any possible recognized chromosomal or hereditary abnormality to be excluded from the study. All the females were examined by a surgeon to catch any possible surgical problem to be excluded from the study. All females were examined by a physician to treat complications like diabetes.

Statistical analysis

Data were analyzed using SPSS version 21 (SPSS, IBM Company, Chicago, IL 60606, USA). Nominal data were compared using Chi-square test. Estimation of odds ratios (ORs) from the stratified analysis was obtained and presented in the Table 1 of this study. OR of >1.5 revealed that defect had an elevated risk. Ninety-five percent confidence intervals (CIs) were calculated using the Mantel-Haenszel method.

Ethical consideration

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients' verbal and analytical approval before the sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee.

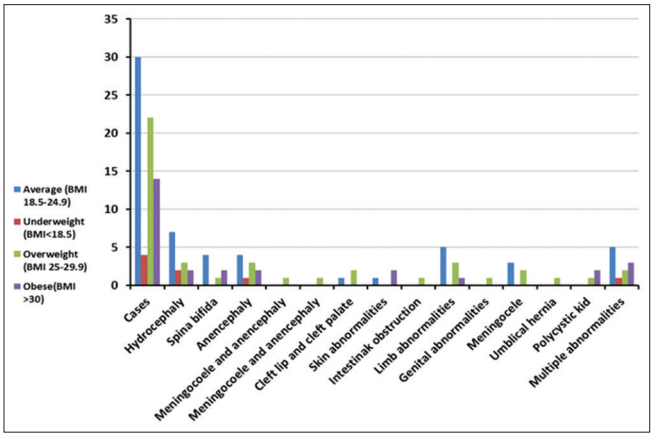

Figure 1: Odd ratio of >1.5 revealed that defect had an elevated risk

Results

One hundred and thirty pregnant women were studied (60 women as control infants and 70 women as case infants). Control group included infants without any congenital malformations.

Table 1 demonstrates the comparison of infant abnormalities between control, average weight women, and obese women; there were more infants with a neural tube defect (33.33%) in obese mothers, especially spina bifida (OR: 3.1, 95% CI: 1.4–11.6) and anencephaly (OR: 2. 9, 95% CI: 0.7–11.4) in comparison to average-weight women. Furthermore, the obese women were more likely to have an infant with hydrocephalic defect (OR: 3.0, 95% Cl:1.4-8.2,Cl:1.1-4.6,Cl:0.8-6.1 in comparison with average-weight women.

In addition, over-weight women have an infant with defects, such as meningocele (OR: 2.2, 95% Cl:1.4-8.2,Cl:1.1-4.6,Cl:0.8-6.1), spina bifida (OR: 2.1; 95% CI: 1.3–7.2), meningocele and hydrocephaly (OR: 2.1; 95% CI: 1–1.0), hydrocephaly (OR: 1.7; 95% CI: Cl:1.4-8.2,Cl:1.1-4.6,Cl:0.8-6.1), meningocele and anencephaly (OR: 1.6; 95% CI: 0.6–3.7), and anencephaly (OR: 1.5: 95% CI: 0.6–5.9).

Multiple abnormalities were also observed to be significantly increased in the obese and overweight mothers (OR: 2.0; 95% CI: 1.1–3.6 and OR: 2.0; 95% CI: 1.1–4.4), respectively, in comparison with normal weight.

There was associated significance difference between overweight and normal BMI women, while there was no statistically significant difference between birth defects and underweight status.

For each of defects for which there was an association among obese women, the ORs for obese and overweight women were greater than that for underweight women [Figure 1].

Pooled ORs for overweight and obese mothers are compared in [Figure 2] and [Table 2] which show an increasing odds of pregnancies affected by neural tube defects, spina bifida (OR: 2.8), anencephaly (OR: 2.3), meningocele and anencephaly

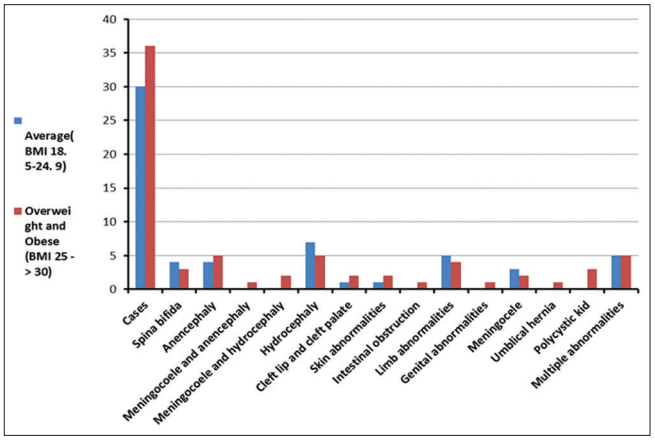

Figure 2: Comparison of cases between average and pooled overweight and obese studied women

Table 1: Odd ratio* for study cases by body mass index category (referent=average weight, body mass index: 18.5-24.9)

Variables	Total	Average (control) (BMI: 18.5-24.9), *n*	Underweight (BMI <18.5)		Overweight (BMI: 25-29.9) (case)		Obese (BMI >30) (case)	
			n	OR* (95%CI)	*n*	OR (95%CI)	*n*	OR (95%CI)
Cases	70	30	4		22		14	
Hydrocephaly	14	7	2	1.1 (0.3-7.1)	3	1.7 (0.8-6.1)	2	3.0 (1.4-8.2)
Spina bifida	7	4	0	-	1	2.2 (1.3-7.2)	2	3.1 (1.4-11.6)
Anencephaly	10	4	1	1.2 (0.3-10.8)	3	1.5 (0.6-5.9)	2	2.9 (0.7-11.4)
Meningocele and anencephaly	1	0	0	-	1	1.6 (0.6-3.7)	0	-
Meningocele and anencephaly	1	0	0	-	1	2.1 (1.1-3.0)	0	-
Cleft lip and cleft palate	3	1	0	1.6 (0.3-7.6)	2	1.4 (0.3-3.4)	0	-
Skin abnormalities	3	1	0	-	0	-	2	1.1 (0.6-3.9)
Intestinak obstruction	1	0	0	-	1	1.2 (0.1-7.4)	0	-
Limb abnormalities	9	5	0	-	3	1.0 (0.5-1.9)	1	0.9 (0.3-1.5)
Genital abnormalities	1	0	0	-	1	1.3 (0.7-3.3)	0	-
Meningocele	5	3	0	-	2	2.2 (1.1-4.6)	0	-
Umblical hernia	1	0		-	1	0.6 (0.5-4.1)	0	-
Polycystic kid	3	0	0	-	1	1.2 (0.6-3.8)	2	1.2 (0.6-3.1)
Multiple abnormalities	11	5	1	1.2 (0.7-2.9)	2	2.0 (1.1-4.4)	3	2.0 (1.1-3.6)

*OR of >1.5 revealed that defect had an elevated risk. OR: Odd ratio, CI: Confidence interval, BMI: Body mass index

Table 2: Comparison of cases between average and pooled overweight and obese studied women

Variables	Total	Average (BMI 18.5-24.9) (control), *n*	Overweight and obese (BMI 25->30)(case)	
			n	OR* (95% CI)
Cases	67	30	36	
Spina bifida	7	4	3	2.8 (1.4-10.4)
Anencephaly	9	4	5	2.3 (0.7-10.3)
Meningocele and anencephaly	1	0	1	1.6 (0.6-3.7)
Meningocele and hydrocephaly	2	0	2	2.1 (1.1-3.0)
Hydrocephaly	12	7	5	2.0 (0.9-7-4)
Cleft lip and cleft palate	3	1	2	1.4 (0.3-3.4)
Skin abnormalities	3	1	2	1.1 (0.6-3.9)
Intestinal obstruction	1	0	1	1.2 (0.1-7.4)
Limb abnormalities	9	5	4	0.9 (0.4-1.6)
Genital abnormalities	1	0	1	1.3 (0.7-3.3)
Meningocele	5	3	2	2.2 (1.1-4.6)
Umblical hernia	1	0	1	0.6 (0.5-4.1)
Polycystic kid	3	0	3	1.2 (0.6-3.4)
Multiple abnormalities	10	5	5	2.1 (1.1-3.1)

*OR of >1.5 revealed that defect had an elevated risk. OR: Odd ratio, CI: Confidence interval, BMI: Body mass index

(OR: 1.6), meningocele and hydrocephaly (OR: 2.1), and meningocele (OR: 2. 2).

Pooled group of overweight and obese mothers also showed that significance increased in the odd of pregnancies affected by multiple abnormalities (OR: 2.0).

Discussion

In our study, Table 2 shows that the risk estimate of OR: 3.1 for spina bifida in obese mothers is approximate to the results of Watkins *et al*.[20] (OR: 3.5), but higher than that of Werler[21] (OR: 2.6).

In our study, overweight mothers were at significantly increased odd of a pregnancy affected by spina bifida compared with mother of normal BMI. In our study (OR: 2.1), this result was much larger than the finding of Watkins *et al*.[20] (OR: 1.5).

Furthermore, in our study, the risk estimate of OR: 2.3 for anencephaly, as shown in Table 2, was higher than OR: 1.12, previously reported by Werler *et al*.[21]

Our study showed that there is no hard relation between orofacial clefts (cleft lip and cleft palate) of infants and overweight women or obese women, as in other studies conducted by Shaw *et al*.[22] who found no evidence of an association between maternal obesity and the risk of pregnancy affected by an orofacial cleft (OR: 1.1).

In our study, there was no association between either maternal overweight or obesity and the risk factor of pregnancy affected by skin abnormalities, intestinal obstruction, limb abnormalities, genital abnormalities, umbilical hernia, and polycystic kidney.

The association between obesity and birth defects is not known, but several possible explanations have been proposed.[23] One explanation might be that obese women have metabolic alterations, such as hyperglycemia or elevated insulin or estrogen levels, that increase their risk for birth defects. Hyperinsulinemia has been shown to be an independent risk factor for neural tube defects, but even after adjustment for hyperinsulinemia, obesity continued to be a modest risk factor.[24] Another explanation is that women who are obese might have diabetes, a known risk factor for birth defects.[25] In previous studies, the relation between obesity and neural tube defects persisted, even when women with known diabetes were excluded or when adjustment was made for diabetes; however, some women with diabetes might be unrecognized.

Conclusions

Our study showed that there is an association between maternal obesity and birth defects. The physiological mechanism(s) behind obesity and birth defects are unknown. In light of these results, it seems unethical to await the elucidation of such mechanism(s) in obese women, and great emphasis needs to be placed on ensuring that reproductive-aged women are of healthy weight preconceptionally.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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