Birth defects associated with obesity

Ovadya Rosenbluh[1,*], Asnat Walfisch[2]

[1]*Obstetrics & Gynecology, The Chaim Sheba Medical Center, Derech Sheba 2, 52 621 Ramat-Gan, Israel*

[2]*Obstetrics & Gynecology, Hadassah Medical Center, 91120 Jerusalem, Israel*

*Correspondence: ovadyar@gmail.com; Ovadia.Rozanblo@sheba.health.gov.il (Ovadya Rosenbluh)

Background: In women of reproductive age, obesity is the most common medical condition. A condition which is increasing in prevalence worldwide. Obesity during pregnancy could have both short- and long-term adverse consequences for both mother and child. *Methods*: In this narrative review we discuss the most prominent observational studies and meta-analyses focusing on the association between maternal obesity (and BMI) and fetal congenital anomalies. Possible pathophysiological pathways linking the two are also discussed. *Results*: Obese women were found to have an increased at-birth prevalence of a wide range of fetal anomalies. These include congenital heart anomalies and neural tube defects, with a possible "dose-response" correlation. The reasons for that may include increased insulin resistance in early pregnancy and nutritional deficiencies, but also probably result from the challenges of fetal anomaly detection during a detailed ultrasound in obese women. *Discussion*: A large array of different fetal anomalies have been found to be increased in the maternal obese population. The incidence of fetal neural tube defects and serious heart anomalies among the obese population might grow by 30%. Congenital anomalies are known to be a major cause of stillbirth and infant mortality, and are important contributors to preterm delivery and childhood morbidity. The possible dose response pattern observed between the severity of obesity and teratogenic potential necessitates further investigation, which may also shed light on the underlying pathophysiology. The increasing prevalence of obesity in general and particularly in the pregnant population may thus have serious health implications. Education regarding the many risks associated with obesity, for mothers and their babies, are warranted.

Keywords

Obesity; Pregnancy; Anomalies

1. Introduction

Rates of obesity are increasing globally, both in developing and developed countries, now considered a global pandemic [1]. An estimated 20% of pregnant women in the United Kingdom and 30% of those in the United States are obese (body mass index [BMI] of over 30 Kg/m^2) [2, 3]. Moreover, it is projected that by 2030, nearly 1 in 2 adults in the United States will suffer from obesity, with nearly a fourth of the adult population suffering severe obesity (BMI > 40) [4]. This dramatic increase in rates of overweight and obese women of childbearing age is of great concern in terms of public health. Evidence accrued from decades of observation and research show that maternal gestational weight gain as well as pre-pregnancy BMI have important effects on maternal and neonatal morbidity and mortality as well as long-term effects on the health of both mother and offspring [5–11]. This includes hypertensive and thromboembolic disorders, gestational diabetes, increased cesarean section rates, and wound infection [12–16]. Fetuses of obese mothers are at increased risk of macrosomia, complicated deliveries, and perinatal death [17–20]. In addition, offspring are at increased risk of developing obesity, hypertension, diabetes, and cardiovascular morbidity in the future [21]. A possible association between maternal obesity and neurodevelopmental disorders, including autism spectrum disorders, and asthma has also been suggested [22].

Finally, some congenital malformations, including congenital heart anomalies and neural tube defects, were shown to be linked with maternal obesity, with a possible "dose-response" correlation [23]. Congenital anomalies are known to be a major cause of stillbirth and infant mortality, accounting for 20% of infant deaths in the United States [24], and are important contributors to preterm delivery and childhood morbidity. North American registries suggest that 3% of all live births in the country are affected by a structural anomaly [25]. Of those, 0.07% births are affected by a neural tube defect and 0.2% by a major heart anomaly. Investigators calculated, in a systematic review and meta-analysis, that the incidence of fetal neural tube defects and serious heart anomalies among the obese population might grow to 0.1% and nearly 0.3%, respectively [26].

In the following chapter we will review the data on various anomalies linked to maternal obesity, and explore potential underlying mechanisms.

2. Neural tube defects

One of the better-known anomalies shown to be correlated with maternal obesity are neural tube defects [27–32], particularly anencephaly and spina-bifida.

A meta-analysis [26] combining data from eighteen studies originating from North America and Europe, which analyzed data from more than 26,000 cases of diverse anomalies

diagnosed in neonates, sought to determine the added risk of maternal obesity to the development of these anomalies. When compared with mothers of normal BMI, the authors found that the OR of developing a neural tube defect in a pregnant obese mother is 1.87 (95% CI, 1.62–2.15; $P = 0.001$). The increased risk was significant also among mothers with BMI greater than 24 but less than 30 (i.e., overweight mothers) by an OR of 1.20 (95% CI, 1.04–1.38; $P = 0.01$).

A potential explanation for this significantly increased risk for NTDs may be related to folate deficiency. Humans cannot produce folate, and the requirement of this vitamin is partly supplied by dietary intake of folate and partly by the use of synthetic folate. Folate is required for cell division and cell maintenance and plays a major role in the re-methylation of plasma homocysteine, which accumulates when meat, fish or plant proteins are digested, to methionine. Homocysteine is neutralized quickly in the human body, as it is a toxic metabolite. When folate levels are reduced, increases in the plasma homocysteine level may cause a delay in the closure of the embryonic neural tube, causing defects in the neural tube [33].

It has previously been established that pregnant women suffering from obesity, also exhibit nutritional deficiencies, specifically reduced folate levels [34, 35]. A study examining the prevalence of micronutrient deficiency in patients with morbid obesity prior to bariatric surgery showed a high prevalence of micronutrient deficiencies, despite energy excess, with common deficiencies being vitamins B12 and D, folate, and iron [36]. Contrary to the belief that obese people consume higher amounts of food and should therefore have sufficient levels of micronutrients, the data demonstrate the reverse. It is postulated that food consumed in the obese population may be of low nutritional value, or, that periods of severe food restriction, undertaken to achieve rapid weight loss, might cause the deficiencies described above. In addition, since obesity is more prevalent among disadvantaged socio-demographic groups, these deficiencies can also be explained by lower health literacy [37].

Importantly, studies conducted at the genetic level have explored the correlation between genes responsible for maternal obesity or maternal hyperglycemia (which are often related) and the development of NTD in the fetus. An American group studying the relationship between the target genes found that when genes responsible for the transport of glucose across the fetal cells (e.g., SLC2A2) interact with the altered maternal LEP and ENPP1 genes (which regulate eating behavior and metabolic rate) they might modify their activity, increasing the risk of NTD in the fetus [38].

3. Cardiovascular anomalies

Obese mothers are at increased risk of having a fetus affected by a cardiovascular anomaly, compared with mothers of recommended BMI [27–29, 39–41]. According to the meta-analysis cited above [26] the odds ratio (OR) of a cardiovascular anomaly in a newborn delivered to an obese mother is 1.30 (95% CI, 1.12–1.51; $P = 0.001$). The cardiac septa de-

fects seem to be the most affected (OR, 1.20; 95% CI, 1.09–1.31; $P = 0.001$), though a trend could also be seen in the incidence of transposition of the great arteries (OR, 1.41; 95% CI, 0.97–2.06; $P = 0.07$).

Additionally, when stratifying the risk of fetal anomalies according to maternal weight class, a "dose-dependent" effect can be observed, with gradually increasing rates of malformations of the nervous system, heart, digestive system, genital organs, and limbs. The relative risk (RR) for congenital heart defects was 1.05 (95% CI, 1.01–1.08) for overweight mothers (BMI 25 to <30) as compared to normal weight mothers (BMI 18.5 to <25), 1.15 (95% CI, 1.09–1.20) for women with class I obesity (BMI 30 to <35), 1.26 (95% CI, 1.16–1.37) among women with class II obesity (BMI 35 to <40), and 1.44 (95% CI, 1.27–1.63) for women with class III obesity (BMI > 40) [42].

Several potential explanations have been suggested for this observed link between maternal obesity and congenital anomalies of the cardiovascular system. One of these involves the correlation between obesity and insulin resistance. When a nondiabetic person consumes an excessive amount of calories and gains weight, the body becomes markedly resistant to the action of insulin. Investigators have shown, using a euglycemic insulin-clamp technique, that tissue sensitivity to insulin declines by up to 40% when an individual becomes 40% over his or her ideal body weight [43]. Insulin resistance will eventually lead to a hyperglycemic environment for the developing embryo, and it is well established that maternal hyperglycemia can potentially cause anomalies in the fetus, most commonly cardiovascular anomalies [44]. The mechanism whereby hyperglycaemia may induce dysmorphogenesis has not been completely elucidated, though several studies have shown that a hyperglycemic environment may cause elevated levels of cell death and apoptosis among the neural crest cells in the developing fetus, leading to the development of a defective fetal heart [45]. Oxidative stress induced by diabetes has been shown to interfere with the process of cardiac neural crest migration at the early stages of organogenesis by inhibiting Pax3 expression, causing cell apoptosis and outflow tract defects [46]. In addition, several authors suggest liberation of free oxygen radicals, deficiency states of myo-inositol or arachidonic acid, and damage to the developing yolk sac, as possible explanations for this association [47]. Therefore, in obese pregnant women, undiagnosed hyperglycemia or diabetes is one potential explanation for the increased risk of congenital cardiac anomalies.

Another possible explanation for the association between obesity and cardiovascular defects could be improper nutrition, as mentioned above. A correlation between maternal vitamin consumption, especially folate, and embryonic cardiac defects have been demonstrated in a number of studies [48, 49]. The same phenomena have been shown to occur in animal studies. In particular, rats with folic acid deficiency were reported to produce cardiac malformed offspring, mostly with defects of the outflow tract, the great ves-

Maternal Obesity

Lower sensitivity to insulin causing a hyperglycemic environment or occult diabetes

Nutritional deficiencies including folate deficiency causing a higher concentration of homocysteine

Lower anomaly detection during detailed US scans resulting in less termination of pregnancy in cases of fetal anomalies
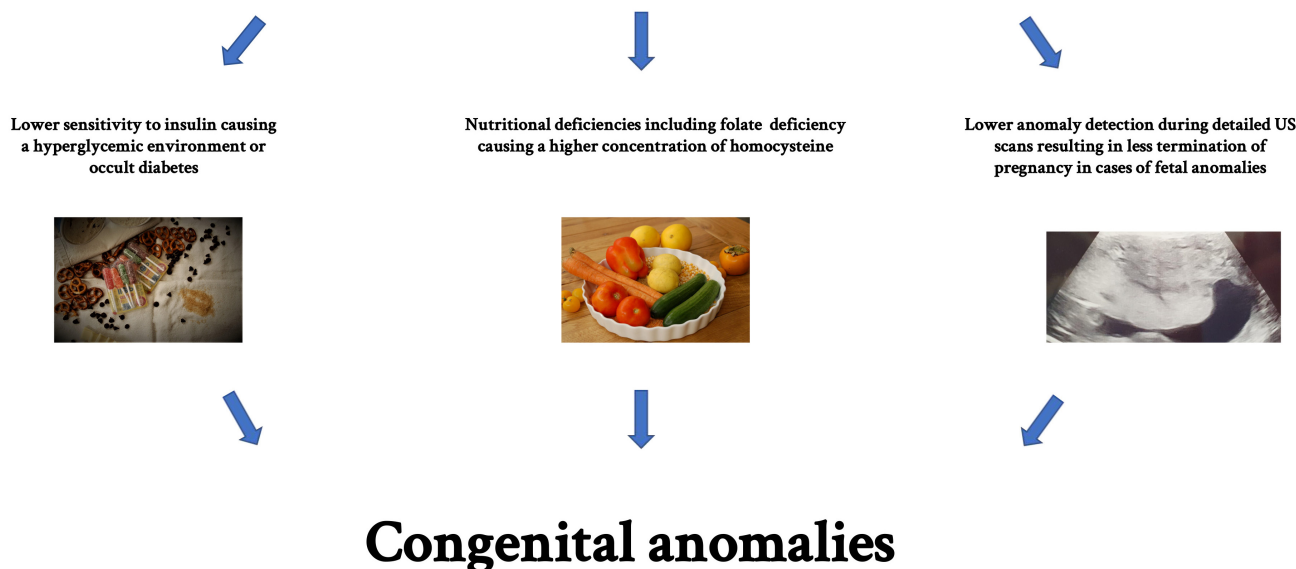
Congenital anomalies

Fig. 1. Pathways linking maternal obesity and congenital anomalies in offspring.

sels and ventricular septal defects [50]. In addition, folic acid deficiency or abnormalities of the metabolism of folic acid and vitamin B12 result in increased levels of homocysteine, shown to induce neural tube and cardiac defects in chick embryos [51].

4. Orofacial clefts

Obese mothers seem to be at an increased risk of having a fetus affected by either a cleft palate or a cleft lip and palate, compared with mothers of recommended BMI [28, 29, 41, 52]. The meta-analysis mentioned earlier [26] found that the OR for the development of a cleft palate was 1.23 (95% CI, 1.03–1.47; P = 0.02), whereas the OR for both a cleft lip and palate was 1.20 (95% CI, 1.03–1.40; P = 0.02). There was no significant increase in risk for the development of a cleft lip alone. However, there have also been a number of studies that did not show an increased risk of orofacial cleft in the fetuses of mothers with obesity [53, 54].

The potential underlying cause leading to the development of these anomalies in the offspring of obese mothers might be the higher prevalence of undetected diabetes or hyperglycemic state, in addition to improper nutrition as previously discussed. Although the risk of orofacial clefts in pregnancies complicated by diabetes has been shown to be elevated, the exact mechanism is unknown [55]. In rats, maternal hyperglycemia has been shown to cause defects in fetal expression of developmental genes) such as the sonic hedgehog gene and bone morphogenetic protein 4 (leading to offspring with different malformations including micrognathia and agnathia, as well as oral clefts [56]. On the other hand, there are conflicting data regarding the role of folic acid deficiency in the development of orofacial deformities [57, 58]. It has been shown that diabetic mothers taking folic acid at the start of their pregnancies had a significant reduction in the risk of orofacial clefts in their offspring when compared to diabetic mothers who did not take folic acid [59]. This might be the result of an altered gene methylation process causing epigenetic changes, thus damaging palatal development [60].

5. Other congenital anomalies

The offspring of mothers with obesity are at a greater risk of developing other congenital anomalies including: anorectal atresia [29, 61], hydrocephaly [28, 29, 61, 62] and limb reduction [29] when compared to mothers with recommended BMI. The OR of these anomalies occurring in the fetuses of obese mothers are 1.48 (95% CI, 1.12–1.97; P = 0.006), 1.68 (95% CI, 1.19–2.36; P = 0.003), and 1.34 (95% CI, 1.03–1.73; P = 0.03), respectively [26]. In addition, a large study done using the Swedish registry showed that maternal obesity is associated with other malformations such as hypospadias (OR, 1.31, 95% CI, 1.17–1.46), cystic kidney (OR, 1.40, 95% CI, 1.03–1.90), pes equinovarus (OR, 1.50, 95% CI, 1.29–1.75), and diaphragmatic hernia (OR, 1.81 95% CI, 1.29–2.55) [61], however these findings were not repeated by others [26]. Finally, several studies have suggested an increased risk of omphalocele [28, 29, 61] as well as a significant protective effect against the development of gastroschisis [29, 61, 63] (OR, 0.17; 95% CI, 0.10–0.30; P = 0.001).

As mentioned above, some of the anomalies described here can be explained by the oxidative stress occurring in pregnant obese women with an altered glucose metabolism. Increased glucose metabolism in fetal cells increases oxida-

Table 1. The fetal anomalies and added risk in the maternally obese population.

Cardiovascular anomalies	OR 1.30 (95% CI, 1.12–1.51)
Septal anomalies	OR 1.20 (95% CI, 1.09–1.31)
Neural tube defects	OR 1.87 (95% CI, 1.62–2.15)
Spina Bifida	OR 2.24 (95% CI, 1.86–2.69)
Anencephaly	OR 1.20 (95% CI, 1.09–1.31)
Orofacial clefts	
Cleft lip and palate	OR 1.20 (95% CI, 1.03–1.40)
Cleft palate	OR 1.23 (95% CI, 1.03–1.47)
Anorectal atresia	OR 1.48 (95% CI, 1.12–1.97)
Hydrocephaly	OR 1.68 (95% CI, 1.19–2.36)
Limb reduction anomalies	OR 1.34 (95% CI, 1.03–1.73)
Omphalocele	OR 1.63 (95% CI, 1.07–2.47)

Data from Stothard *et al.* and Waller *et al.* [26, 44]. CI, confidence interval; OR, odds ratio.

tive stress, which in turn inhibits the expression of Pax3 in neuroepithelial cells, preventing the accumulation of p53 protein- a tumor-suppressor protein. Low levels of p53 activate genes causing apoptotic cell death. Neuroepithelium suffering an excess of cell death fails to proliferate and migrate, leading to an open neural tube or a cardiac malformation, among other potential anomalies [46].

In addition to the potential etiologies described above, another possible explanation for the increased at-birth prevalence of some of these anomalies is the technical difficulty in preforming ultrasound scanning in obese women. It has been shown that adipose tissue may attenuate ultrasonic signals [64] in addition to increasing the distance between the transducer and the fetus being investigated, thus affecting image quality. Previous studies have found that obese women may be at twice the risk of suboptimal sonographic visualization during detailed fetal anatomy scanning, than women of normal body habitus [65]. This technical difficulty may potentially result in fewer terminations of pregnancy for fetal anomalies and increased prevalence at birth.

6. Conclusions

The offspring of pregnant women suffering from obesity are at increased risk of a wide range of congenital anomalies (Table 1). These anomalies may include neural tube defects, cardiovascular anomalies, oral clefts, and limb reduction anomalies. The exact etiology of this increased risk is not clear, but evidence suggests that two potential explanations: nutritional deficiencies (especially folic acid deficiency) and an undiagnosed hyperglycemic maternal environment. In addition, it is possible that the technical difficulty of detailed fetal anomaly scanning in obese gravitate, results in less frequent pregnancy terminations and therefore more fetal anomalies at birth (Fig. 1). The possible dose response pattern observed between the severity of obesity and teratogenic potential necessitates further investigation, which may also shed light on the underlying pathophysiology.

The increasing prevalence of obesity in general and par-

ticularly in the pregnant population may thus have serious health implications, not only to the parental generation but also to generations to come. Education regarding the many risks associated with obesity, for mothers and their babies, coupled with pre-pregnancy weight loss programs, may reduce the magnitude of this worrisome phenomenon.

Author contributions

OR and AW conceived of the study, performed the literature search and have written and edited the manuscript.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

Funding

Conflict of interest

The authors declare no competing interests.

References

[1] Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, *et al.* Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014; 384: 766–781.

[2] Heslehurst N, Rankin J, Wilkinson JR, Summerbell CD. A nationally representative study of maternal obesity in England, UK: trends in incidence and demographic inequalities in 619 323 births, 1989–2007. International Journal of Obesity. 2010; 34: 420–428.

[3] American College of Obstetricians and Gynecologists. ACOG Committee opinion no. 549: obesity in pregnancy. Obstetrics & Gynecology. 2013; 121: 213–217.

[4] Ward ZJ, Bleich SN, Cradock AL, Barrett JL, Giles CM, Flax C, *et al.* Projected U.S. state-level prevalence of adult obesity and severe obesity. New England Journal of Medicine. 2019; 381: 2440–2450.

[5] Catalano PM, Ehrenberg HM. The short- and long-term implications of maternal obesity on the mother and her offspring. BJOG: An International Journal of Obstetrics and Gynaecology. 2006; 113: 1126–1133.

[6] Sebire NJ, Jolly M, Harris JP, Wadsworth J, Joffe M, Beard RW, *et al.* Maternal obesity and pregnancy outcome: a study of 287,213 pregnancies in London. International Journal of Obesity and Related Metabolic Disorders. 2001; 25: 1175–1182.

[7] Johansson S, Villamor E, Altman M, Bonamy AE, Granath F, Cnattingius S. Maternal overweight and obesity in early pregnancy and risk of infant mortality: a population based cohort study in Sweden. British Medical Journal. 2014; 349: g6572.

[8] Yu Z, Han S, Zhu J, Sun X, Ji C, Guo X. Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: A systematic review and meta-analysis. PLoS ONE. 2013; 8: e61627.

[9] Mamun AA, O'Callaghan M, Callaway L, Williams G, Najman J, Lawlor DA. Associations of gestational weight gain with offspring body mass index and blood pressure at 21 years of age: evidence from a birth cohort study. Circulation. 2009; 119: 1720–1727.

[10] Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH.

Competing risks model in screening for preeclampsia by maternal characteristics and medical history. American Journal of Obstetrics and Gynecology. 2015; 213: 62.E1–62.E10.

[11] Syngelaki A, Bredaki FE, Vaikousi E, Maiz N, Nicolaides KH. Body mass index at 11–13 weeks' gestation and pregnancy complications. Fetal Diagnosis and Therapy. 2011; 30: 250–265.

[12] Chauhan SP, Magann EF, Carroll CS, Barrilleaux PS, Scardo JA, Martin JN. Mode of delivery for the morbidly obese with prior cesarean delivery: vaginal versus repeat cesarean section. American Journal of Obstetrics and Gynecology. 2001; 185: 349–354.

[13] Chu SY, Callaghan WM, Kim SY, Schmid CH, Lau J, England LJ, et al. Maternal obesity and risk of gestational diabetes mellitus. Diabetes Care. 2007; 30: 2070–2076.

[14] Usha Kiran TS, Hemmadi S, Bethel J, Evans J. Outcome of pregnancy in a woman with increased body mass index. BJOG: An International Journal of Obstetrics and Gynaecology. 2005; 112: 768–772.

[15] O'Brien TE, Ray JG, Chan W. Maternal body mass index and the risk of preeclampsia: a systematic overview. Epidemiology. 2003; 14: 368–374.

[16] van Hoorn J, Dekker G, Jeffries B. Gestational diabetes versus obesity as risk factors for pregnancy-induced hypertensive disorders and fetal macrosomia. Australian & New Zealand Journal of Obstetrics & Gynaecology. 2002; 42: 29–34.

[17] Nuthalapaty FS, Rouse DJ. The impact of obesity on obstetrical practice and outcome. Clinical Obstetrics and Gynecology. 2004; 47: 898–913.

[18] Robinson H, Tkatch S, Mayes DC, Bott N, Okun N. Is maternal obesity a predictor of shoulder dystocia? Obstetrics & Gynecology. 2003; 101: 24–27.

[19] Salihu HM, Dunlop A, Hedayatzadeh M, Alio AP, Kirby RS, Alexander GR. Extreme obesity and risk of stillbirth among black and white gravidas. Obstetrics & Gynecology. 2007; 110: 552–557.

[20] Rössner S, Öhlin A. Maternal body weight and relation to birth weight. Acta Obstetricia et Gynecologica Scandinavica. 1990; 69: 475–478.

[21] Whitaker RC. Predicting preschooler obesity at birth: the role of maternal obesity in early pregnancy. Pediatrics. 2004; 114: e29–e36.

[22] Krakowiak P, Walker CK, Bremer AA, Baker AS, Ozonoff S, Hansen RL, et al. Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. Pediatrics. 2012; 129: e1121–e1128.

[23] Cai G, Sun X, Zhang L, Hong Q. Association between maternal body mass index and congenital heart defects in offspring: a systematic review. American Journal of Obstetrics and Gynecology. 2014; 211: 91–117.

[24] Heron M, Hoyert D, Xu J, Scott C, Tejada-Vera B. Deaths: preliminary data for 2006. National Vital Statistics Report. 2008; 56: 1–52.

[25] California Birth Defects Monitoring Program Report of Birth Defects 2012–2016. Available at: https://www.cdph.ca.gov/Programs/CFH/DGDS/CDPH%20Document%20Library/CBDMP%20Documents/Summary%20Birth%20Defect%20Prevalence%20Table.pdf (Accessed: 10 March 2021).

[26] Stothard KJ, Tennant PWG, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies. The Journal of the American Medical Association. 2009; 301: 636–650.

[27] Waller DK, Mills JL, Simpson JL, Cunningham GC, Conley MR, Lassman MR, et al. Are obese women at higher risk for producing malformed offspring? American Journal of Obstetrics and Gynecology. 1994; 170: 541–548.

[28] Watkins ML, Rasmussen SA, Honein MA, Botto LD, Moore CA. Maternal obesity and risk for birth defects. Pediatrics. 2003; 111: 1152–1158.

[29] Waller DK. Prepregnancy obesity as a risk factor for structural birth defects. Archives of Pediatrics & Adolescent Medicine. 2007; 161: 745–750.

[30] Watkins ML, Scanlon KS, Mulinare J, Khoury MJ. Is maternal obesity a risk factor for anencephaly and spina bifida? Epidemiology. 1996; 7: 507–512.

[31] Werler MM, Louik C, Shapiro S, Mitchell AA. Prepregnant weight in relation to risk of neural tube defects. The Journal of the American Medical Association. 1996; 275: 1089–1092.

[32] Hendricks KA, Nuno OM, Suarez L, Larsen R. Effects of hyperinsulinemia and obesity on risk of neural tube defects among Mexican Americans. Epidemiology. 2001; 12: 630–635.

[33] Czeizel AE, Dudás I, Vereczkey A, Bánhidy F. Folate deficiency and folic acid supplementation: the prevention of neural-tube defects and congenital heart defects. Nutrients. 2013; 5: 4760–4775.

[34] Casanueva E, Drijanski A, Fernández-Gaxiola AC, Meza C, Pfeffer F. Folate deficiency is associated with obesity and anemia in Mexican urban women. Nutrition Research. 2000; 20: 1389–1394.

[35] Hötzel D. Suboptimal nutritional status in obesity (selected nutrients). Bibliotheca Nutritio et Dieta. 1986; 37: 36–41.

[36] Krzizek E, Brix JM, Herz CT, Kopp HP, Schernthaner G, Schernthaner G, et al. Prevalence of micronutrient deficiency in patients with morbid obesity before bariatric surgery. Obesity Surgery. 2018; 28: 643–648.

[37] Wamala SP, Wolk A, Orth-Gomér K. Determinants of obesity in relation to socioeconomic status among middle-aged Swedish women. Preventive Medicine. 1997; 26: 734–744.

[38] Lupo PJ, Mitchell LE, Canfield MA, Shaw GM, Olshan AF, Finnell RH, et al. Maternal-fetal metabolic gene-gene interactions and risk of neural tube defects. Molecular Genetics and Metabolism. 2014; 111: 46–51.

[39] Watkins ML, Botto LD. Maternal prepregnancy weight and congenital heart defects in offspring. Epidemiology. 2001; 12: 439–446.

[40] Cedergren M, Selbing A, Källén B. Geographic variations in possible risk factors for severe cardiac malformations. Acta Paediatrica. 2002; 91: 222–228.

[41] Cedergren M, Källén B. Maternal obesity and the risk for orofacial clefts in the offspring. Cleft Palate-Craniofacial Journal. 2005; 42: 367–371.

[42] Persson M, Cnattingius S, Villamor E, Söderling J, Pasternak B, Stephansson O, et al. Risk of major congenital malformations in relation to maternal overweight and obesity severity: cohort study of 1.2 million singletons. British Medical Journal. 2017; 357: j2563.

[43] DeFronzo RA, Ferrannini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidaemia and atherosclerotic cardiovascular disease. Diabetes Care. 1991; 14: 173–194.

[44] Becerra JE, Khoury MJ, Cordero JF, Erickson JD. Diabetes mellitus during pregnancy and the risks for specific birth defects: a population-based casecontrol study. Pediatrics. 1990; 85: 1–9.

[45] Wang X, Li S, Wang G, Ma Z, Chuai M, Cao L, et al. High glucose environment inhibits cranial neural crest survival by activating excessive autophagy in the chick embryo. Scientific Reports. 2015; 5: 18321.

[46] Morgan SC, Relaix F, Sandell LL, Loeken MR. Oxidative stress during diabetic pregnancy disrupts cardiac neural crest migration and causes outflow tract defects. Birth Defects Research Part A: Clinical and Molecular Teratology. 2008; 82: 453–463.

[47] Reece EA, Homko CJ, Wu YK. Multifactorial basis of the syndrome of diabetic embryopathy. Teratology. 1996; 54: 171–182.

[48] Scanlon KS, Ferencz C, Loffredo CA, Wilson PD, Correa-Villaseñor A, Khoury MJ, et al. Preconceptional folate intake and malformations of the cardiac outflow tract. Epidemiology. 1998; 9: 95–98.

[49] Botto LD, Mulinare J, Erickson JD. Occurrence of congenital heart defects in relation to maternal multivitamin use. American Journal of Epidemiology. 2000; 151: 878–884.

[50] Rosenquist TH, Ratashak SA, Selhub J. Homocysteine induces congenital defects of the heart and neural tube: effect of folic acid. Proceedings of the National Academy of Sciences of the United

States of America. 1996; 93: 15227–15232.

[51] Mulinare J, Cordero JF, Erickson JD, Berry RJ. Periconceptional use of multivitamins and the occurrence of neural tube defects. The Journal of the American Medical Association. 1988; 260: 3141–3145.

[52] Blanco R, Colombo A, Suazo J. Maternal obesity is a risk factor for orofacial clefts: a meta-analysis. British Journal of Oral & Maxillofacial Surgery. 2015; 53: 699–704.

[53] Richards ID. Congenital malformations and environmental influences in pregnancy. Journal of Epidemiology & Community Health. 1969; 23: 218–225.

[54] Shaw GM, Todoroff K, Schaffer DM, Selvin S. Maternal height and prepregnancy body mass index as risk factors for selected congenital anomalies. Paediatric and Perinatal Epidemiology. 2000; 14: 234–239.

[55] Spilson SV, Kim HJ, Chung KC. Association between maternal diabetes mellitus and newborn oral cleft. Annals of Plastic Surgery. 2002; 47: 477–481.

[56] Ejdesjö A, Wentzel P, Eriksson UJ. Influence of maternal metabolism and parental genetics on fetal maldevelopment in diabetic rat pregnancy. American Journal of Physiology Endocrinology and Metabolism. 2012; 302: E1198–E1209.

[57] Shaw GM, Lammer EJ, Wasserman CR, O'Malley CD, Tolarova MM. Risks of orofacial clefts in children born to women using multivitamins containing folic acid periconceptionally. Lancet. 1995; 346: 393–396.

[58] Czeizel AE, Timar L, Sakozi A. Dose-dependent effects of folic acid on the prevention of orofacial clefts. Pediatrics. 1999; 104: e66.

[59] Correa A, Gilboa SM, Botto LD, Moore CA, Hobbs CA, Cleves MA, et al. Lack of periconceptional vitamins or supplements that contain folic acid and diabetes mellitus-associated birth defects. American Journal of Obstetrics and Gynecology. 2012; 206: 218.e1–218.e13.

[60] Seelan RS, Mukhopadhyay P, Pisano MM, Greene RM. Developmental epigenetics of the murine secondary palate. ILAR Journal. 2012; 53: 240–252.

[61] Blomberg MI, Källén B. Maternal obesity and morbid obesity: the risk for birth defects in the offspring. Birth Defects Research Part A: Clinical and Molecular Teratology. 2010; 88: 35–40.

[62] Anderson JL, Waller DK, Canfield MA, Shaw GM, Watkins ML, Werler MM. Maternal obesity, gestational diabetes, and central nervous system birth defects. Epidemiology. 2005; 16: 87–92.

[63] Lam PK, Torfs CP, Brand RJ. A Low Prepregnancy body mass index is a risk factor for an offspring with gastroschisis. Epidemiology. 1999; 10: 717–721.

[64] Taniguchi DK, Martin RW, Myers J, Silverstein FE. Measurement of the ultrasonic attenuation of fat at high frequency. Academic Radiology. 1994; 1: 114–120.

[65] Khoury FR, Ehrenberg HM, Mercer BM. The impact of maternal obesity on satisfactory detailed anatomic ultrasound image acquisition. Journal of Maternal-Fetal & Neonatal Medicine. 2009; 22: 337–341.