

CONTEMPORARY REVIEW

Maternal Obesity and Diabetes Mellitus as Risk Factors for Congenital Heart Disease in the Offspring

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ABSTRACT: Congenital heart disease (CHD) is the most common anatomical malformation occurring live-born infants and an increasing cause of morbidity and mortality across the lifespan and throughout the world. Population-based observations have long described associations between maternal cardiometabolic disorders and the risk of CHD in the offspring. Here we review the epidemiological evidence and clinical observations relating maternal obesity and diabetes mellitus to the risk of CHD offspring with particular attention to mechanistic models of maternal-fetal risk transmission and first trimester disturbances of fetal cardiac development. A deeper understanding of maternal risk factors holds the potential to improve both prenatal detection of CHD by identifying at-risk pregnancies, along with primary prevention of disease by improving preconception and prenatal treatment of at-risk mothers.

Key Words: cardiometabolic ■ congenital heart disease ■ maternal diabetes mellitus ■ maternal obesity

Among anatomical malformations present at birth, congenital heart disease (CHD) is the most common, occurring in 0.8% to 1% of live-born infants, and is increasing in prevalence worldwide.¹ In the current practice of neonatal and pediatric cardiothoracic surgery and perioperative care, the survival of children with CHD approaches 95% to 99% depending on the severity of disease.² However, childhood survivors of CHD are impacted by neurodevelopmental differences,³ whereas adult survivors of CHD are burdened with adult-onset cardiovascular disease,⁴ neuropsychiatric disease,⁵ and cancer.⁶ From infancy through adulthood, CHD continues to be an important and increasing proportion of the population at increased risk of morbidity and mortality.

Although the past decade has seen advances in our understanding of the genetic basis of CHD,⁷ maternal diabetes mellitus occurring during early pregnancy has been recognized as a risk factor for disease for many decades.⁸ More recently, population-based observations have described associations between risk of CHD in the offspring with other maternal cardiometabolic disorders such as obesity.⁹ The significant

phenotypic overlap between diabetes mellitus, obesity, and cardiometabolic risk is complex; it is not yet established which of these factors is causal for risk to the fetus when present in the mother during early pregnancy (Figure).

GENERAL RELATIONSHIP: MATERNAL OBESITY

Mirroring trends in the general population, both the rate and severity of maternal obesity has increased at an alarming rate during recent years.¹⁰ In European countries, 7% to 25% of expectant mothers are overweight,¹¹ and in the United States only 45% of mothers have a normal weight when becoming pregnant.¹⁰

Maternal obesity is associated with adverse pregnancy outcomes, neonatal complications, and morbidity. These include stillbirth,¹² macrosomia,^{13,14} shoulder dystocia,¹⁴ preterm delivery,¹⁵ and congenital malformations, such as neural tube defects,^{16,17} omphalocele,^{17,18} and CHD.^{17–22} Moreover, a dose-dependent association has also been observed whereby severity

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of maternal obesity is directly associated with risk for adverse neonatal outcomes.^{9,23}

Several recent meta-analyses consistently report a general association between maternal overweight and obesity and risk for congenital heart defects in the offspring.^{24–26} The increased risk associated with maternal obesity includes a wide range of different cardiac defects, including septal defects,^{9,22,27} aortic arch defects,⁹ persistent ductus arteriosus,^{9,21} conotruncal defects,^{9,27–30} left ventricular outflow tract obstruction defects,²⁹ and right ventricular outflow tract defects.^{21,28} The association of risk regarding specific CHD subtypes, however, has not been universally consistent in different studies. One source of bias could be the fact that body mass index (BMI) estimations in many of these studies were based on retrospective or self-reported data, which are associated with recall bias. In addition, many of the studies report only prenatally or neonatally diagnosed defects. Given that noncritical CHD may not cause symptoms at birth and diagnosed later in life, these studies might be under-reporting CHD rates. Finally, many of the studies are case-control studies, which provide estimates of risk that may be less reliable than prospective, population-based cohort studies for estimating prevalence.

The largest single study thus far, including a national cohort of 2 050 491 live-born singleton infants

in Sweden, showed that maternal obesity measured at the first antenatal visit increased the risk to offspring for transposition of great arteries in those with a BMI of 35 to 40 and >40 kg/m², aortic arch defects in those with a BMI of 30 to 35, 35 to 40, and >40 kg/m², single-ventricle heart in a group of mothers with a BMI of 30 to 35 kg/m², and atrial septal defect and patent ductus arteriosus in mothers with a BMI of >25 kg/m². In addition, the risk for pulmonary valve defects was increased in offspring of mothers with a BMI of 30 to 35 kg/m².⁹ The strengths of this study included a population-based design with prospectively collected data on both exposure and outcome in a country with publicly funded health care, but did not take into account pregnancies with CHD that resulted in termination or stillbirth.

The risk for CHD also appears to increase with the severity of obesity. The study by Persson et al from Sweden demonstrated that the risk for congenital malformations, including CHD, progressively increased with BMI from overweight to severe obesity.³¹ When focusing on specific CHD groups, aortic arch defects, atrial septal defect, and patent ductus arteriosus presented with a dose-responsive association.⁹ In addition, a similar dose-responsive association has been reported in hypoplastic left heart syndrome and right outflow tract defects.²¹

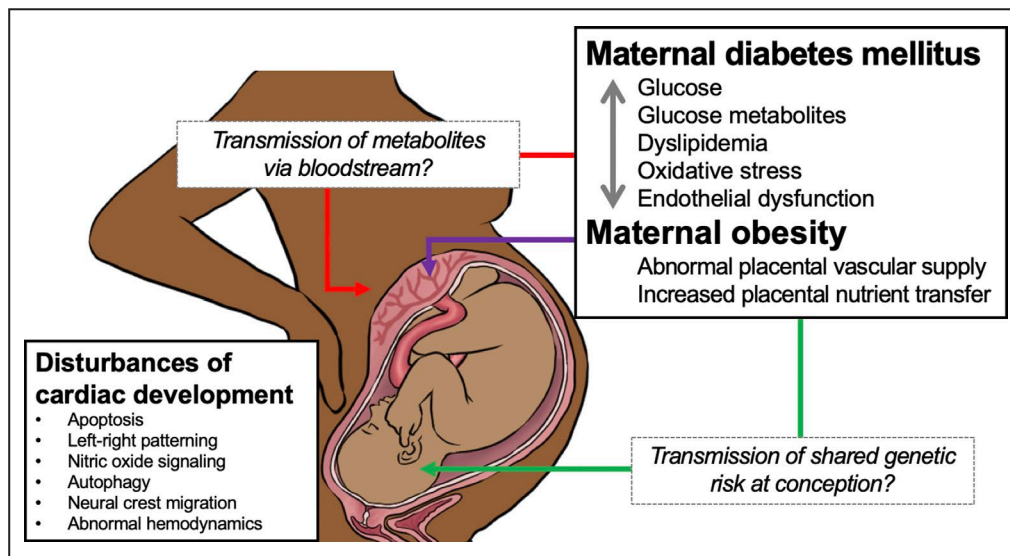


Figure. Potential mechanisms for transmission of maternal metabolic risk for congenital heart disease (CHD) in the fetus.

Illustration of potential mechanisms of transmission of maternal factors during pregnancy influencing risk for CHD in offspring. Maternal diabetes mellitus and obesity share a variety of intermediate phenotypes (bidirectional gray arrow), which could be transmissible from mother to fetus in the blood across the placenta (red arrow) or transmitted genetically at the time of conception by pleiotropic variants, conferring risk for both metabolic phenotypes and CHD (green arrow). Specific differences in placental function related to maternal obesity may also contribute to risk (purple arrow). Experimental models have suggested a variety of potential mechanisms by which maternal metabolic factors may disturb development of the heart, which occurs early in pregnancy during the first trimester.

POTENTIAL MECHANISMS OF RISK IN MATERNAL OBESITY

The precise mechanism by which maternal obesity impacts critical stages of cardiac development is not known and is hypothesized to be multifactorial. Whereas the mechanisms of maternal obesity in later gestation on placental function and fetal growth have been under active research during recent years, early pregnancy has received less attention.

Maternal prepregnancy obesity is known to be associated with increased risk for gestational diabetes mellitus,³² and it is likely that some of the effect in obese individuals may be mediated by glycemic dysregulation. However, the CHD-risk increase has remained significant even after adjusting for glucose levels, suggesting that abnormalities in glucose metabolism do not fully explain the risk in obese mothers.²⁷ In addition to glycemic dysregulation, a wide range of metabolic abnormalities are present in obese individuals. Obesity is associated with hyperinsulinemia and insulin resistance,^{33,34} dyslipidemia,^{33,35} and oxidative stress.³⁵ In pregnancy, gestational diabetes mellitus increases low-density lipoprotein susceptibility to oxidation, and obesity has been further shown to exacerbate this effect.³⁶ Compared with nonobese women, obese mothers may display differential fat distribution, where non-obese women accumulate fat in the lower body whereas obese women accumulate fat in the upper body.³⁷ Upper-body obesity is associated with reduced uptake and storage of fatty acids, along with increases in lipolysis.³⁸ In contrast, lower-body fat accumulation is associated with more-favorable lipid and carbohydrate metabolic dysregulation³⁹ and an overall lower-risk metabolic profile.⁴⁰ Thus, the potential negative effects of adverse metabolic changes related to fat accumulation during pregnancy are more profound in obese individuals, which may contribute to increased levels of adverse effects in the fetus.

Fetal macrosomia associated with maternal obesity has been proposed to arise from an increased placental nutrient transfer, related, at least partly, to adiponectin levels. Circulating adiponectin levels are lower in obese individuals⁴¹ and remain lower in obese individuals throughout pregnancy.⁴² Lower adiponectin levels during pregnancy have been associated with placental insulin resistance^{43,44} and adverse placental function, in terms of increased placental nutrient transfer^{45–47} and increased fetal growth.⁴⁸ Development of the pancreas and production of insulin do not occur until the beginning of the second trimester; therefore, during the period of heart development during the early first trimester, the fetus is unable to regulate glucose and

may be susceptible to adiponectin-related dysfunction in placental glucose transport.⁴⁹

Endothelial cell dysfunction in mice lacking endothelial nitric oxide synthase during embryogenesis has been shown to cause CHD in mice.^{50,51} Obesity causes chronic pre-existing endothelial activation and impairment of endothelial function,^{33,52–54} as well as inflammatory upregulation.³³ Bioavailability of nitric oxide, a regulator of vascular tone, is decreased in endothelial cell dysfunction. Insulin⁵⁵ and adiponectin⁵⁶ activate endothelial nitric oxide synthase, whereas in obesity and diabetes mellitus these protective mechanisms are diminished. Maternal obesity is associated with increased abnormalities in placental vascular supply, and it has been shown to have an adverse effect on fetal vascular circulation.⁵⁷ Thus, the endothelial dysregulation present in obese mothers may extend to the fetal circulation to impact developmental pathways in the fetus. Moreover, the effect may persist after birth, given that it has been observed that offspring of nonhuman primates exposed to a high-fat diet during pregnancy have impaired endothelial function >1 year after birth.⁵⁸

Finally, it has been proposed that some of the CHD risk increase is mediated by a lower diagnostic rate in pregnancy screenings in obese individuals, given that cardiac views during pregnancy are suboptimal in obese mothers. Decreased sensitivity of ultrasound for cardiac anatomy has been documented in obese mothers.^{59–61} Whereas rates of pregnancy termination are difficult to ascertain and compare between studies, it is possible that differences in diagnostic rates could affect termination rates, leading to a higher share of CHD pregnancies carried to birth in obese mothers with lower diagnostic rates. However, in a recent study of an advanced nation-wide CHD screening program within a country with universal health coverage, obesity or other maternal risk factors for offspring severe heart disease did not appear to affect prenatal detection as such.³⁰

IMPACT OF TREATMENT AND PRENATAL CARE

Lifestyle interventions aiming to restrict weight gain in obese women during pregnancy are seen as a means to reduce adverse outcomes related to obesity. A healthier diet during the year before pregnancy has been shown to decrease the risk for conotruncal and septal defects in the offspring,⁶² and one-carbon-rich dietary pattern during pregnancy, characterized by a high intake of fish and seafood, has been associated with a reduced risk of overall CHD.⁶³ Maternal malnutrition and especially folate deficiency has been associated with CHD in the offspring,⁶⁴ and

there is evidence that obese mothers may have an insufficient response to folic acid supplementation for primary prevention of congenital anomalies.^{65,66} Lifestyle interventions for expectant mothers with obesity and/or previous gestational diabetes mellitus during pregnancy have not, however, resulted in an effect on gestational weight gain, or obstetric or perinatal outcomes.⁶⁷ It has been suggested that obesity could be associated with a lower compliance for following nutritional recommendations.⁶⁸ Moreover, prepregnancy BMI is a stronger predictor for adverse outcomes as compared with gestational weight gain.⁶⁹ These results indicate that lifestyle interventions should be increasingly aimed at mothers planning pregnancy. Interestingly, certain genetic risk variants have been shown to modify the effectiveness of lifestyle interventions,⁷⁰ which might affect targeting of such interventions in the future.

Several animal studies have addressed interventions to improve the outcome of obese pregnancies. Exercise has been shown to prevent adverse effects of maternal obesity on placental vascularization and fetal growth.⁷¹ In a mouse model, exercise in obese pregnancy was beneficial to offspring cardiac function and structure.⁷² Adiponectin levels are lower in obese mothers, and adiponectin supplementation of mice during late pregnancy reversed the adverse effects of maternal obesity on placental function and fetal growth.^{73,74} Moreover, although these interventions showed to be beneficial in terms of maternal and fetal health, none of these studies specifically addressed CHD as an outcome.

GENERAL RELATIONSHIP: GLYCEMIC REGULATION

The association between maternal diabetes mellitus and CHD in offspring has been recognized for almost 80 years.⁸ The underlying pathology of diabetes mellitus is a mismatch between insulin production and response to insulin resulting in elevated glucose levels. Type 1 diabetes mellitus is attributable primarily to the absence of pancreatic insulin secretion originating from autoimmune destruction of beta cells. Type 2 and gestational diabetes mellitus arise from an increased requirement for insulin for intracellular transport of glucose in peripheral tissues, a now well-described physiological phenomenon of insulin resistance implicated in the pathophysiology of a variety of adult-onset diseases.⁷⁵ Maternal diabetes mellitus is a risk factor for adverse maternal and fetal outcomes, including anatomical malformations such as CHD.^{76,77} Risk for CHD in offspring is present in mothers with all types of disease, such as type 1^{78,79} or 2^{79,80} diabetes mellitus existing before pregnancy,

along with gestational diabetes mellitus developing during pregnancy.^{81,82}

In large, population-based studies, maternal diabetes mellitus appears to be a strong risk factor for any and all subtypes of CHD.^{81,83} Individual studies hint at a higher risk for conotruncal and laterality subtypes of CHD^{83,84}; however, comparisons between subtypes are limited by low prevalence of individual malformations present even in large cohorts. For syndromic causes of CHD with a known genetic etiology, such as Down syndrome, maternal diabetes mellitus is not recognized as a cofactor for cardiac malformation in the fetus.⁸⁵ On a population level, exposure to prepregnancy diabetes mellitus was estimated to be responsible for up to 4.2% of CHD within a regional Canadian health system.⁸⁰

Cardiac development occurs during the first trimester and is largely complete by the sixth week of pregnancy; thus, maternal physiology and metabolism during the early first trimester is most relevant to the developing fetal heart. Hemoglobin A1C values measured during the first trimester are associated with risk for CHD in offspring,^{86,87} and women with pre-existing diabetes mellitus who experienced a greater number of diabetic complications or had a greater hemoglobin A1C appear to be at increased risk of having a child with CHD.^{78,83} Our own recent data suggest that risk for CHD extends to pregnancies of women who may not carry a clinical diagnosis of diabetes mellitus; abnormalities of glucose metabolism below standard diagnostic thresholds for diabetes mellitus are associated with measurable risk for CHD in offspring.^{88,89} Thus, risk of CHD in offspring is directly correlated with abnormalities in glucose metabolism in pregnancies with and without diabetes mellitus.

MECHANISM OF RISK

The mechanism by which presence of maternal diabetes mellitus during critical stages of cardiac development is not clear. The earliest experiments simply treated chicken and rodent embryos with exogenous glucose, which resulted in malformations in many organ systems including cardiac defects.^{90,91} Experimentally supported mechanisms proposed to alter cardiac development include glucose-mediated disturbances of left-right patterning,⁹² increased apoptosis resulting from oxidative or other cellular stress,^{93,94} deficiencies in nitric oxide signaling,⁹⁵ impaired autophagy,⁹⁶ and alterations of neural crest cell formation and migration.^{97,98} Deriving from early descriptions of the teratogenic potential of glucose alone, *ex vivo* models of cardiac development have substituted treatment with supraphysiological levels

of glucose as a proxy for maternal diabetes mellitus. However, alterations in maternal glucose are accompanied by changes in downstream metabolites of glycolysis, such as beta-hydroxybutyrate,⁹⁹ and the impact of downstream metabolites of glucose upon cardiac development remains relatively unexplored.^{100–102} Accompanying these mechanistic hypotheses, experimental models of maternal diabetes mellitus have also described the disruption of canonical signaling pathways during mesodermal differentiation and cardiac development.¹⁰³ The variety of proposed cellular models and molecular mechanisms, none of which are mutually exclusive, highlights the need for further research into how maternal diabetes mellitus disturbs fetal heart development (Figure).

IMPACT OF TREATMENT AND PRENATAL CARE

Like maternal obesity, maternal diabetes mellitus is associated with a variety of adverse pregnancy outcomes, including pre-eclampsia, prematurity, fetal demise, and stillbirth.⁷⁷ These outcomes have prompted public health efforts to improve preconception and prenatal diagnosis and treatment for diabetes mellitus. In a meta-analysis studying prenatal care, standard treatment of maternal diabetes mellitus resulted in ~75% reduction in risk of anatomical malformations in offspring inclusive of CHD.¹⁰⁴ Newer technological approaches to diabetes mellitus care, including continuous glucose monitoring and continuous subcutaneous insulin injection, are in common use by women of childbearing age,¹⁰⁵ and randomized controlled trials using these technologies demonstrate incremental improvements in measures of glucose control and improvements in some measures of pregnancy and fetal outcome.¹⁰⁶ Simulations suggest that in the US population, achieving glycemic control in all women before pregnancy has the potential to reduce rates of CHD by 3.8% or 2670 cases per year.¹⁰⁷

In addition to standard care of diabetes mellitus before and during pregnancy, other routine interventions have been trialed in pregnant women with maternal diabetes mellitus with the goal of preventing adverse fetal and maternal outcomes. Exercise during pregnancy is safe and reduces maternal glucose levels,¹⁰⁸ but there is inadequate evidence to assess any impact of maternal exercise on fetal outcomes.¹⁰⁹ Trials to gauge the impact of dietary interventions during pregnancy upon maternal and fetal outcomes are ongoing.¹¹⁰ Conversely, observational studies suggest that exposure to either metformin or beta-blockers during pregnancy, both of which reduce glucose levels, may

actually increase the risk of certain types of CHD in the fetus.^{111,112} In summary, routine adjunctive interventions targeted at glucose reduction in maternal diabetes mellitus have yet to demonstrate improvements in fetal outcomes, such as CHD, in appropriately controlled trials.

Novel interventions centered on proposed mechanisms of disease have arisen from experimental animal models of maternal diabetes mellitus. Pharmacological agents, which ameliorate oxidative stress, have been reported to prevent cardiac malformations; in a chick model of maternal diabetes mellitus, coinjection of N-acetyl cysteine with glucose prevented heart malformations caused by injection of glucose alone.¹¹³ In a mouse model of type 1 diabetes mellitus, neural tube defects (also associated with maternal diabetes mellitus) were prevented by maternal ingestion of trehalose, a polysaccharide with antioxidant properties.¹¹⁴ Nitric oxide is a key vascular signaling molecule synthesized in the smooth muscle and endothelium, which is disturbed in diabetes mellitus¹¹⁵; oral supplementation of diabetic mice with a cofactor for nitric oxide synthase reduced the rates of CHD in offspring.⁹⁵ However, given the observation that even clinically accepted interventions to reduce maternal glucose fail to impact the rate of fetal malformations during pregnancy and an absence of consensus on the mechanism of risk, the prospect of prenatal interventions derived from experimental animal models should be viewed with caution.

KNOWLEDGE GAPS AND FUTURE DIRECTIONS

CHD causes high levels of physical, emotional, and economic burden for the patient, their family, and society at large. Although maternal obesity and glucose metabolism are clearly associated with the risk of CHD, the mechanisms by which risk is transmitted from mother to fetus and the causal factors which disturb fetal cardiac development remain poorly defined (Figure). Understanding the causal factors and mechanism of transmission will provide the necessary framework for addressing 2 important real-world outcomes; primary prevention of CHD and improving prenatal screening for CHD.

Given that neonatal and childhood surgery are likely to be the mainstay of treatment for the foreseeable future, and that cardiopulmonary bypass and perioperative disturbances in physiology may contribute to the adverse health outcomes in long-term survivors of CHD,^{116,117} primary prevention of disease is an important goal with potentially significant benefit to public health. Obesity and diabetes mellitus are both potentially modifiable maternal risk factors for CHD,

each with effective evidence-based therapies generally and in the context of maternal health.^{118,119} With a clear understanding of the mechanism of risk transmission from mother to fetus, large-scale trials of public health interventions focused upon causal factors underlying maternal obesity and glucose metabolism with specific attention to fetal outcomes are needed. Where possible, fetal outcomes data inclusive of cardiac malformations should be scrutinized from ongoing trials of dietary interventions¹¹⁰ and innovations in glucose control¹⁰⁶ in order to guide efforts prospective interventions for CHD. Lifestyle factors, such as weight, physical activity, and dietary habits, represent potential targets for preconception and prenatal interventions for CHD prevention.

A key component of prenatal care is the in utero identification of pregnancies with CHD as early as possible. An improved understanding of the maternal risk factors for carrying a pregnancy impacted by CHD holds the potential to improve both prenatal screening and postnatal care. Improved risk stratification of pregnant women may allow for better selection of pregnancies at the greatest risk of CHD for prenatal screening by fetal echocardiogram,¹²⁰ particularly in health systems with less-organized screening programs.^{30,121} In pregnancies with CHD which are carried to term,¹²² prenatal detection also allows early referral to a tertiary center to optimize the delivery and early care, and thus improved prenatal screening is likely to improve early survival and long-term outcomes of children affected with CHD.^{123,124}

Although the significance of maternal glucose metabolism and obesity as risk factors for CHD is clear, the mechanisms underlying these risks are not. A deep mechanistic understanding of causal maternal factors holds the potential to improve both prevention of CHD by preconception and prenatal treatment of causal maternal factors, and to improve prenatal screening and in utero identification of CHD by measuring causal maternal factors to identify pregnancies at highest risk. The molecular mechanisms of maternal risk and potential genetic modifiers of these factors represent an outstanding opportunity where advances from basic, translational, and clinical research are poised to yield real-world applications to reduce the burden of disease.

ARTICLE INFORMATION

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Disclosures

None.

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