Cardiology in the Young

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Infants of diabetic mothers: epidemiology, pathophysiology, fetal heartassessment, structural and functional heart consequences: A narrative review

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Review

Cite this article: Shati AA, Mahmood SE, Alqahtani YA, Al-Qahtani SM, Bushari TM, and Parvez A (2024) Infants of diabetic mothers: epidemiology, pathophysiology, fetal heartassessment, structural and functional heart consequences: A narrative review. *Cardiology in the Young* **34**: 2068–2073. doi: 10.1017/S1047951124036394

Received: 11 October 2023
Revised: 29 September 2024
Accepted: 11 November 2024

Keywords:
cardiac structure; gestational diabetes; infant of diabetic mother; fetus; pregnancy; prenatal

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Abstract

Infants of diabetic mothers are neonates born to a woman who had periodic hyperglycaemia during pregnancy. Consequently, infants of diabetic mothers are at higher risks of illness besides morbidity and mortality due to teratogenic effects on the fetal cardiovascular system, causing most frequent CHDs. The primary purpose of this review is to present, on this topic, a better-comprehended review covering pertinent material and data to be informed of severe risks to a newborn's cardiac system and function. These conditions can affect maternal, fetal, neonatal, and future adult health. Further research should be addressed towards the early detection of diabetes, its magnitude, and management. Immediate interventions should be proposed to lessen the diabetes burden and its adversative effects during the prenatal period.

Introduction

An infants of diabetic mothers (IDMs) is a baby who is born to a mother with experience of periodic hyperglycaemia in the course of pregnancy. The mother's condition could lead to risky hyperglycaemia. Consequently, the creation of growth factors triggers fetal development and shows deposition of subcutaneous fats rather than glycogen.[1–3] Diabetes in pregnant women could be pregestational or gestational (in 80% of the cases); it is considered disadvantageous in pregnancy and perinatal periods.[3] Diabetes can lead to early limit of growth and a higher risk of congenital abnormalities in the initial trimester, selective organomegaly, macrosomia, slower vital nervous system evolution during the second trimester, and chronic hypoxaemia, and even death. Although the perinatal fatality rate of infants of diabetic mothers has decreased over recent years, it continues to be significant problem compared with the general society.[4]

Serious hereditary complications are presented in about 5 to 8% of newborns of diabetic parents.[5] In consequence, infants of diabetic mothers are at higher risk of illness in addition to mortality linked to teratogenic effects on the fetal cardiovascular system, including most frequent CHDs that are considered the leading cause of newborns and fetal cardiomyopathy.[6,7] This teratogenic effect of maternal diabetes[8,9] can be attributed to the higher incidence of congenital malformations among the newborns of diabetic mothers than that of the general population.[10,11] Pregnant women with pregestational diabetes mellitus have 4–5 times increased risk of fetal cardiac malformations and even death than non-diabetic mothers.[4,12] Cardiac malformations are the most common type of malformations occurring in about 8.5% of such cases, which is about 10 times more than its incidence in the normal population (0.8%).[13–17] In a cohort study, poor glycaemic control of pregestational diabetes generated 5.6% of CHDs in newborns.[18] Another experimental study on mice showed that pre-existing diabetes caused CHD in 58% of the offsprings.[19] Besides, the prevalence of cardiomyopathy was found up to 40% in infants of diabetic mothers.[2] Pregnancies with pre-existing diabetes might cause the hypertrophy of myocardial cells, and functional impairment, which also have long-standing sequelae on the circulatory system of the infants.[20] The serum concentrations of cardiac injury markers, cardiac troponin I, were significantly elevated and correlated with different forms of cardiomyopathy.[2] Newborns of mothers with poorly controlled diabetes could also have significant complications from compromised heart functions, including congestive cardiac dysfunction.[21] Maternal diabetes does have a causal association with increased cardiovascular disease rates in offsprings, the prevention, screening, and treatment of diabetes in women of childbearing age could help to reduce the risk of cardiovascular disease in the next generation.[22]

Previous reviews provide information on the association of maternal diabetes with cardiac manifestations in infants on a broader scale. Accordingly, the main purpose of this article is to present, on this topic, a better-comprehended review covering pertinent material and data to be informed of serious risks on newborn's cardiac lesions and functions.

Methods

This narrative review addresses the research question of what is the relationship of maternal diabetes with cardiac manifestations in infants. Key repositories were examined to find the pertinent scientific papers that were available for such analysis. The search queries, used singly and in conjunction, are "Maternal diabetes," "Infants," "Newborns," "Infants of Diabetic Mothers," "IDMs," "Cardiac manifestations," "Epidemiology," "Pathophysiology," and "Congenital heart disease." Only English-language articles have been included in this narrative review. Ethical review and approval were waived for this study because it does not directly involve human subjects (secondary research study).

Epidemiology

Gestational diabetes is high blood sugar (diabetes) that starts or is first detected during pregnancy. Most commonly, women with gestational diabetes mellitus are diagnosed using an oral glucose tolerance test at 24 to 28 weeks of gestation, the time of routine screening. For women with pregestational Diabetes Mellitus (DM), glucose control in early pregnancy is vital to a normal organogenesis, necessitating early prenatal care; thereafter patients should see a clinician approximately every 2 weeks to optimise their glucose control.

Furthermore, pregestational diabetes could be Type 1 or Type 2 in the prenatal period, where Type 2 diabetes is usually connected with more adverse events.[23,24] A UAE retrospective cohort study reported that maternal diabetes Type 1 may cause more CHDs in infants of diabetic mothers compared to maternal diabetes type.[25] The gestational diabetes mellitus prevalence rate has rapidly elevated up to 53.4% in recent years, which may be attributed to the new diagnostic methods.[26,27] The prevalence rate varies according to the population; some countries are at low risk (Sweden with <2% and the USA with 4.8%), while others have a higher risk (Canada with 17.8% and France with 12.1%). Middle East countries have similarly higher prevalence rates, such as 20.6% in UAE, and 16.3% in Qatar.[28]

In a multicentre cohort study in Saudi Arabia (RAHMA), recruiting 9723 pregnant women, 24.2% had gestational diabetes whereas 4.3% had pregestational diabetes.24 These findings were consistent with the preceding studies from the Middle East and other countries.[29–31]

Older maternal age and obesity in pregnant women are well-known risk factors. These factors accompany the increased prevalence of pregestational diabetes besides adverse perinatal outcomes.[25,31–33] Genetic factors, socio-economic disparities, and racial differences or ethnicity influence the prevalence of CHDs among infants of diabetic mothers. This may be due to suboptimal blood glucose control of hyperglycaemia caused by unaffordable and demanding access to healthcare services.[34]

Pathophysiology

The pathogenesis of hyperglycaemia in infants inducing cardiac defects is still not fully understood. Previous studies were mainly experiments on animals, whereas human studies were limited to observational documents reporting only hypotheses on the association between diabetic mothers and a higher risk of developing fetal cardiac abnormalities.[35] The common cardiac defects involve the great arteries, including truncus arteriosus, and double outlet right ventricle, which are found to be more prevalent in infants of diabetic mothers.[36,8] Normal cardiac development during pregnancy needs insulin for cardiac mass development using cell proliferation and insulin-like growth factor *I*.[37] In diabetic women, the high concentration of glucose transferred through the placenta triggers fetal hyperinsulinemia and increases serum levels of growth factors, such as Insulin-like growth factor-1 (IGF-1), resulting in septal hypertrophy.[7,38] The long-lasting fetal hyperinsulinemia may raise the total body weight of the fetus and cause discerning organomegaly consequent to the hypertrophy of the insulin-sensitive tissues, including the heart and affinity of insulin receptors.[39]

It has been reported that newborns from diabetic mothers with poor or good glycaemic management may develop ventricular septal hypertrophy of the heart.[40] Thus, fluctuation in the expression of CHD, due to maternal diabetes, is ramified. This could be attributed to reactive oxygen species (ROS), which impact heart structure by influencing cell migration, proliferation, apoptosis, and differentiation pathways. ROS also mediate alterations in molecular pathways involved in cardiac development, such as Wnt, Notch, TGF-β, and HIF-1α, as a result of maternal hyperglycemia and associated oxidative stress. Additionally, epigenetic mechanisms may modify the expression of critical genetic material essential for heart development.[41,42]

The placental disorder is mainly caused by the placenta vessels variation resulting from poor glycaemic management of maternal diabetes or other causes. It can result in fetal cardiac dysfunction.[43,44] The type of diabetes significantly influences placental vascular development. Gestational diabetes primarily affects the late second trimester, impacting angiogenesis and microvascular remodeling, but it does not influence earlier stages of development. In contrast, pregestational diabetes can affect the entire placental and fetal development process, including vasculogenesis.[45]

Another pathomechanism is that infants of diabetic mothers may inherit intrauterine growth retardation, which in turn can enhance the risk of cardiovascular disorder throughout life.[46,20] Infants of diabetic mothers cause numerous adverse events, together with complex metabolic and endocrine disturbances. It can cause respiratory distress, and birth trauma and can even lead to admissions to neonatal ICUs (NICUs).[47]

Fetal heart assessment

After birth, the heart function is usually evaluated using echocardiography with M-mode by quantifying the fractional echocardiography with left ventricles. These measurements are ejection phase indicators of systolic activity and are used to determine accurately cardiac manifestations even in adults. However, several studies reported that M-mode and additional conventional markers, including fractional shortening, are relatively insensitive in the fetus and may present some difficulties.[48,49] The myocardial performance index is considered a widely used alternative method to reflect systolic and diastolic myocardial activity using the ratio of (isovolumic contraction time with isovolumic relaxation time)/ejection time. In infants, myocardial performance index is based on blood flow Doppler.[6] (Table 1)

https://doi.org/10.1017/S1047951124036394 Published online by Cambridge University Press

Table 1. Assessment parameters of fetal cardiac function

Conventional parameters	Age-dependent	Heart rate-dependent	Right Ventricle
M-mode	No	No	No
Fractional area shortening	No	No	No
Inflow Doppler (blood flow)	Yes	Yes	Yes
MPI from blood flow Doppler	Maybe	No	Yes

Table 2. Type of CHDs in infants of diabetic mothers in different countries

CHDs	Bangladesh (56)	Pakistan (58)	Saudi Arabia (59)	Egypt (2)
Atrial septal defects	77.4%	8.9%	5%	–
Ventricular septal defects	35.5%	12.9%	4%	–

A heart murmur is one of the most used tools in detecting CHD; however, its presence or absence is not definitive for a normal or abnormal blood flow of the heart. A study showed that 61.3% of neonates with diabetic mothers presenting with low murmur in the first days of life have structural heart defects.[50]Two-dimensional speckle-tracking echocardiography could offer an additional benefit over conventional echocardiography to detect subclinical unfavourable changes in myocardial function in this population.[51,52,53]

Structural heart defects

There are different complexities on the anatomopathological level, resulting in more or less severe pathophysiological consequences. CHD has been presented as a gross heart defect or great vessel transposition at birth. For this reason, early diagnosis of CHD with the optimal intervention plays a critical part, and in some of these cases, is lifesaving. According to the severity and site of the lesion, the clinical findings of CHD can differ, and the most frequent manifestations are respiratory distress, cyanosis, feeding difficulties, and poor cardiac output.[50]

The fetal cardiac malformation is a broad definition that primarily includes atrial septal defect, ventricular septal defect, transposition of great arteries, patent ductus arteriosus, patent foramen oval, and hypertrophic cardiomyopathy.[48,49] Atrial septal defect, patent ductus arteriosus, ventricular septal defect, and patent foramen oval account for the highest percentage in prevalence and can differ according to the geographic region (Table 2).[2,54,56,57]

Hyperglycaemia during pregnancy can prevent the expression of genes that are responsible for the septation of the conotruncus in the neural crest cells. The absence of their expression can inhibit the septation of the conotruncus resulting in cardiac outflow tract disorders such as truncus arteriosus, tetralogy of Fallot, outflow tract occlusion, and transposition of great arteries. It has been proven in different studies that infants of diabetic mothers have a higher risk of developing ventricular septal defects (Table 3); they are at significant risk of all types of intracardiac defects.[35,55] Furthermore, an experimental study on embryonic chick showed that mutations in cellular proliferation in the endocardial cushions all through the crucial phases of cardiac development contribute to malformations in the outflow tract, resulting in modifications in blood flow patterns and leading to imperative abnormalities in the vasculature.[58]

Table 3. Comparative table of ventricular septal defect prevalence in different countries

Country	Ventricular septal defects in IDMs (%)
Togo	24,4
Senegal	38
Senegal	23,3
West Africa	37
Burkina-Faso	50
France	30–40
United States	30
Burkina	28,2

Functional heart defects

As about 90% of the cardiac lesions can be identified prenatally, detailed fetal echocardiography in all diabetic women during pregnancy has been recommended.[59,60,61] Heart rhythm is theorised as a predictor for the early detection of infant cardiac manifestations in gestational diabetes.[62] Tachycardia is one of the less common presentations in infants of diabetic mothers reported.[63]

Fetal hypertrophic cardiomyopathy is the most frequent disorder that mutates cardiac functions due to fetal hyperinsulinism, sometimes resulting in the obstruction of left ventricular outflow.[64,65]

Diastolic dysfunction is another fetal heart function defect resulting from pregestational diabetes. It is mainly induced by pathological interventricular septal hypertrophy. This impaired filling of the ventricle can appear in a range between 20 and 30% of diabetic pregnancies. It is detected when the E/A ratio is abnormal through mitral or tricuspid valve inflow, along with a higher isovolumetric relaxation time, using conventional Doppler imaging. The septal wall thickening causes rapid ventricular filling, creating mitral inflow disorder.[66,67] Serious intrauterine myocardial hypertrophic modifications can also cause diastolic dysfunction in infants of diabetic mothers.[68]

Maternal diabetes could result in important adverse perinatal manifestations other than heart defects that can be related to each other such as macrosomia, acute respiratory distress syndrome, birth trauma, transient tachypnoea, cyanosis, and metabolic and

https://doi.org/10.1017/S1047951124036394 Published online by Cambridge University Press

Table 4. Select recent studies reporting cardiac findings in the offspring of diabetic mothers

Study Reference	Study Design	Country	Study population	Cardiac findings
Bogo et al.[72] (2021)	Prospective, descriptive observational	Brazil	48 children of mothers with gestational diabetes mellitus	Decreased rate of myocardial hypertrophy and changes in cardiac function parameters in the fetal and neonatal periods due to adequate clinical control were observed.
Depla 2021[75]	Systematic review and meta-analysis	Worldwide	2276 controls and 1925 women with pregnancy affected by diabetes mellitus (DM).	1120 had GDM, 671 had PDM and in 134 cases diabetes type was not specified. Fetal cardiac hypertrophy was more prevalent in diabetic pregnancies than in non-diabetic controls in 21/26 studies, and impaired diastolic function was observed in diabetic pregnancies in 22/28
D'Ambrosi et al. 2021[76]	Observational	Italy	35 women with a GD and 217 non-diabetic.	Right ventricular filling time (RVFT) was significantly lower in the GD group (mean of RVFT = 39.2 ± 4.4 versus 43.6 ± 4.6; $p < 0.01$). Likewise, left ventricular filling time (LVFT) was shorter in the GD group compared to the non-GD group, though the difference was not significant (mean of LVFT = 43.6 ± 4.6 versus 44.6 ± 5.5; $p = 0.33$).
Papazoglou et al. 2021[73]	Systematic review and meta-analysis	Worldwide	Total population (n = 12,461,586), 79,476 women with PGDM and 160,893 with GDM	Both GDM and PGDM significantly increaseed the risk of CHD in comparison with the general population. PDGM has a greater association with CHD, being correlated with a 3.5-fold increase in the risk of malformation.
Smith et al. 2021[74]	Case Control	Ireland	40 infants of mothers with GDM and 40 control infants.	Infants of mothers with GDM demonstrate important changes in myocardial function in addition to pulmonary vascular resistance
Di Bernardo et al. 2022[77]	Cohort	Switzerland	Gestational diabetes mellitus ($n = 123$) without Gestational diabetes mellitus ($n = 141$)	Newborns of mothers with or without GDM had similar clinical characteristics and LV mass. Some echocardiographic differences were detected.
Lookzadeh et al. 2022[78]	Cross-sectional	Iran	150 neonates of mothers with diabetes	The prevalence of CHD in IDMs was 12.7%. Significant relationship between maternal uncontrolled diabetes and a high incidence of CHD in IDMs was observed ($P \leq 0.0001$).

endocrine disorders.[51,69,70] Infants of poorly controlled diabetic mothers showed a significant reduction in left ventricular global strain rate, higher incidence of neonatal hypoglycaemia, prolonged neonatal ICU stay, and persistent fetal transitional cardiac shunt in comparison to infants of adequately controlled diabetic mothers.[53] In another case-control study, between-group infant cardiac function was determined. Intraventricular pressure difference and intraventricular pressure gradient, using M-mode Doppler imaging, were higher in Infant of Gestational Diabetic Mother (IGDM) than in the controls, as well as the global circumferential strain by speckle-tracking echocardiography technology was also higher in IGDM than in the controls.[71]

Therefore, a strong association between maternal diabetes and cardiovascular disease in infants is established (Table 4).[72–78] Diabetes prevention, screening, and treatment among women of reproductive age could help to reduce the risk of cardiovascular disease in infants.[22]

Conclusion

The rising incidence of pregestational and gestational diabetes significantly impacts maternal, fetal, neonatal, and future adult health. It is crucial to pursue further research that explores the prevalence of diabetes in pregnancy, its management, and the interventions that can reduce the burden of diabetes during the prenatal period. Such efforts are essential to mitigate the adverse effects associated with diabetic pregnancies and improve health outcomes for both mothers and their children in the long term.

Data availability statement. Not applicable.

Acknowledgement. None.

Financial support. The authors extend their appreciation to the Deanship of Scientific Research at King 294 Khalid University for funding this work through a large group Research Project under grant 295 number RGP2/189/45.

Author contribution. Conceptualisation, A.A.S.; methodology.; formal analysis, A.A.S.; investigation A.A.S. and S.M.A.; data curation, A.A.; writing—original draft preparation, A.A.S and S.E.M.; writing—review and editing S.E.M and A.A.S,; visualisation, Y.A.A. and T.M.B.; supervision, A.A.S.; project administration, A.A.S.. All authors have read and agreed to the published version of the manuscript.

Competing interests. The authors declare no conflict of interest.

Institutional review board statement. Ethical review and approval were waived for this study due to it not directly involving human subjects (secondary research study).

Informed consent statement. The study itself was a review article and did not involve human subjects and hence patient consent was waived.

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