Review Article

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EVALUATION OF FOETAL CARDIAC DYSFUNCTION AS A CAUSE OF UNEXPLAINED STILL-BIRTH IN DIABETIC PREGNANCIES

Ayesha Ahmad*, Fareha Khatoon*, Amrita Singh*, Sushma Verma, Saambhavi***

Department of Obstetrics and Gynaecology, Department of Personalised and Molecular Medicine***

Era's Lucknow Medical College & Hospital, Sarfarazganj, Lucknow, U.P., India-226003

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Address for correspondence
Dr. Fareha Khatoon
Department of Obstetrics and Gynaecology
Era's Lucknow Medical College & Hospital, Lucknow-226003
Email: faarehak@gmail.com
Contact no: +91-9838777497

ABSTRACT

The prevalence of diabetes in pregnancy has risen in the past few decades across the globe. Along with it, maternal and perinatal complications have also increased. Still-birth remains an important complication and till date, largely unexplained. As the pathogenesis is unclear, we are still not able to predict babies at higher risk of still-birth. Recent studies have focused on cardiac dysfunction as a probable causative factor. The present review was conducted to consolidate the existing information about cardio-dynamics and discuss its role in causation of still-birth in diabetic pregnancies. Electronic databases were searched using relevant MeSH terms for original articles, meta-analysis, case reports, case series and standard guidelines issued by maternal and foetal medicine societies. Still-birth remains an important area of research in diabetic pregnancies. Foetal cardiac studies may help in development of prediction models for prognostication of foetuses at high risk of still-birth.

KEYWORDS: Diabetes in pregnancy, Gestational Diabetes, Hyperglycemia, Cardiac diastolic dysfunction, Foetal Myocardial Performance Index.

INTRODUCTION

Diabetic pregnancies have seen an exponential rise in the past few decades on a global basis (1). According to Indian data (2013) around 6 million women in India had some form of hyperglycemia in pregnancy, of which 90 % were Gestational Diabetes (GDM) (2). The estimated prevalence of GDM (3) in India has been variously reported as 7.7% (Swami et al; 2008) (4) ; 18.5% (Bhavadharini et al; 2016) (5) ; 27% (Nayak et al; 2013) (6) ; 34.9% (Arora et al; 2014) (7) and 42% (Gopalakrishnan et al; 2015) (8) . In comparison to their Caucasian counterparts, Indian women have been found to have a much higher risk of developing glucose intolerance in pregnancy (11 times higher). With such high prevalence, the incidence of maternal and foetal complications also escalates. (9) (Table 1) One of the most important and unexplained territory remains the increased risk of still-birth associated with maternal hyperglycemia. Despite a lot of research on the subject, till date, almost half of the still-births remain unexplained. As data accumulates exploring the reasons of still-birth in diabetic pregnancies, we have realised that changes in foetal cardiovascular system might have an important role to play in the pathogenesis of still-births.

This review aims to consolidate the existing information about foetal cardiac dysfunction as a cause of unexplained still-birth.

Neonatal hyperbilirubinemia
Macrosomia
Fetal growth restriction
Neonatal hypocalcemia
Congenital malformations
Respiratory distress syndrome
Neonatal polycythemia
Still birth
Others: Shoulder dystocia, Erb's palsy, Neonatal hypoglycemia, Cardiomyopathy

Table 1: Common Fetal and Perinatal Complications of Diabetic Pregnancies

Data Identification

We searched the electronic databases using relevant MeSH terms for original articles, meta-analysis, case reports, case series and guidelines issued by maternal and foetal medicine societies. The search was limited to PubMed, Medline, Elsevier and Cochrane Library databases and restricted to article in English language, from 1990 to 2019 January and confined to humans.

Perinatal Morbidity Associated With Maternal Diabetes

There is abundant literature demonstrating the association of maternal hyperglycaemia in the periconceptional period with an increased risk of foetal cardiac malformation. However, we have reasonable data to show that even in the absence of structural malformation, maternal hyperglycaemia predisposes to altered foetal cardiac function; which has been advanced as a possible cause contributing to sudden still-birth in diabetic pregnancies. However, due to scant literature on the subject, the correlation between maternal glycemic levels, foetal cardiac status and risk of still-birth has not been established in detail. Whereas some researchers have observed that the risk of adverse cardiac function is lower in women with GDM who have a good glycemic control (Lindegaard et al;2008)(10), others have found that foetal cardiac wall thickness, cardiac systolic and diastolic functions are affected by GDM independent of glycemic control (Ren et al;2011) (11) Therefore, although accepted that cardiac dysfunction does occur in diabetic pregnancies, the extent to which maternal blood sugar levels contribute to the pathophysiology is debatable.

Pathogenesis of Foetal Cardiac Abnormalities in Diabetic Mothers

The mechanism of foetal cardiac injury has been studied by many investigators. It is suggested that maternal hyperglycaemia may be associated with inflammation of myocardial tissue and ventricular free walls, foetal hyperinsulinism and hypertrophy of the myocardium by increased fat and protein synthesis. Some papers suggest that foetal hyperinsulinemia is primarily responsible for myocardial hypertrophy and diastolic dysfunction. (Mohsin et al, 2019) (12).

It is further hypothesised that intrauterine exposure to a hyperglycaemic environment may cause epigenetic changes resulting in adverse foetal myocardial remodelling. (Miranda et al, 2017)(13) High blood sugar levels have been shown to affect biochemical processes in the foetus, for instance, induction of placental genes related to chronic stress and inflammation leading to embryopathy and deleterious effects on the foetal cardiovascular system. Of the different cardiac tissues, myocardium and the inter-ventricular septum (IVS) are most commonly affected by maternal hyperglycemia. The ventricular free walls are relatively less affected (14).

Assessment of Foetal Cardiac Function:

Foetal two-dimensional echocardiography is a standard screening tool for evaluation of cardiac anatomy and function during pregnancy. (Ren et al, 2011) (11). It is recognised for having a high sensitivity and specificity in detection of foetal congenital heart defects. Its role in diagnosing foetal cardiac dysfunction is still evolving.

Myocardial Performance Index (MPI) is an important parameter to assess cardiac function, which is non invasive and independent of heart rate and ventricular geometry. (Mohsin et al, 2019)(12) It is a pulsed wave Doppler derived index and is a global indicator of cardiac function. It utilises cardiac time intervals to assess right or left ventricular myocardial performance. The diastolic phase consists of two components: ventricular relaxation and atrial systole. Ventricular relaxation occurs during iso-volemic phase and during early rapid filling of the ventricle. A raised MPI is an early marker of foetal cardiac dysfunction (15).

Tissue Doppler Imaging (TDI) has been studied by investigators as a supplement to routine foetal echocardiography. It is used to measure high intensity and low velocity echoes of myocardium, enabling recognition of systolic and diastolic interdependency. (Lindegaard and Nielsen, 2008)(10) it is seen as a future tool for evaluation of foetal cardiac diastolic function, especially because it is relatively independent of heart rate and heart load.

Foetal Cardiac Abnormalities in Diabetic Pregnancies:

Both structural and functional abnormalities have been found in foetuses of diabetic mothers. Commonly associated are hypertrophic cardiomyopathy, pericardial effusion and abnormal foetal heart rate patterns. The major cardiac changes noted in foetuses were diastolic dysfunction, higher peak velocities of aortic and pulmonary outflow tracts , raised Pulmonary Vein Pulsatility Index (PVPI) and increased MPI. (Pilania et al; 2016)(16)

Myocardial hypertrophy is commonly seen and leads to increased ventricular stiffness resulting in decreased diastolic ventricular filling and systolic cardiac function. Myocardial hypertrophy usually resolves as foetal insulin levels normalise, which may take a few months. Nevertheless, some neonates may present with cardiomegaly and respiratory distress as a result of poor left ventricular compliance. (Mohsin et al, 2019)(12).

Miranda et al [(2017)(13) conducted a cross-sectional study comparing foetal cardiac function in 76 pregnancies with maternal diabetes to 53 healthy pregnancies. They found thicker foetal IVS with maternal diabetes and lower early diastolic strain rate and late diastolic strain rate for both ventricles on deformation analysis. Similarly, Ren et al (11) concluded that foetal cardiac wall thickness is increased

and diastolic function impaired in women with GDM, irrespective of maternal glycemic control. Wong et al, (17) found LV hypertrophy as an additional finding.

Studies have been conducted comparing cardiac function in fetuses of healthy mothers and foetuses of mothers with GDM (FGDM) and found significant diastolic dysfunction in FGDM. The authors have suggested that GDM impairs ventricular function even in the absence of pathological myocardial hypertrophy. (Balli et al, 2013) (18) and Mohsin et al, 2019 (12).

Can we predict adverse perinatal outcome on the basis of foetal cardiac function?

As the evidence stands today, we need further research focussed on the study of foetal cardio-dynamics in diabetic pregnancies before a risk prediction model can be developed which flags at-risk fetus. Russell et al (2008) followed up 26 diabetic pregnancies and observed that ultrasonographic evidence of altered cardiac function precedes cardiac structural changes. Presently, the antenatal care module in diabetic pregnancies incorporates foetal echocardiography at 22 weeks of gestation to evaluate the cardiac structural defects. However, as evidence is accumulating implicating altered foetal cardiac function with maternal hyperglycaemia, we need more studies evaluating both structure and functioning of foetal heart. There is further need to correlate the data with maternal hyperglycaemia and perinatal outcomes.

Tissue Doppler Imaging has been suggested as an important adjunct to assess cardiac function. Foetal TDI and its application in foetal cardiac functional assessment in foetuses of diabetic mothers has not been analysed by many authors. (Ren et al, 2011)(11). Preliminary data is forthcoming and its incorporation in routine foetal echocardiography may help in tailoring antenatal care.

CONCLUSION

Still-birth remains an important area of research in diabetic pregnancies. Foetal cardiac studies may give an insight into this grey area and give a new dimension to management of diabetic pregnancies. Development of prediction models will further strengthen the prognostication of fetuses at high risk of still-birth.

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