Introduction

Diabetes mellitus in pregnancy increases the risk of numerous complications in the neonate, including both structural and functional cardiovascular diseases. Infants of pregestational diabetics, especially those with poor glycemic control, are significantly more likely to have a congenital heart malformation than those of non-diabetics ***(Jenny et al., 2017).***

Cardiovascular abnormalities in infants of diabetic mothers occur in the form of congenital heart diseases (3-5%), and cardiomyopathy (10-20%) ***(Correa et al., 2012).***

Even infants of diabetic mothers (IDMs) with structurally normal hearts may develop transient myocardial hypertrophy and associated systolic and diastolic dysfunction ***(Kozák-Bárány et al., 2004)***. It is suggested that fetal hyperinsulinism may trigger hyperplasia and hypertrophy of myocardial cells by increasing fat and protein synthesis ***(Correa et al., 2012).***

The Tissue Doppler imaging (TDI) method depicts myocardial motion (measured as tissue velocity) at specific locations in the heart. Tissue velocity indicates the rate at which a particular point in the myocardium moves toward or away from the transducer. Integration of velocity over time yields displacement or the absolute distance moved by that point ***(Theodore et al., 2007).***

Altered systolic function has been well documented in IDMs. TDI and two-dimensional echocardiography was done in a group of symptomatic and asymptomatic IDMs, noting impaired global longitudinal strain, abnormal cardiac torsion, and lower MV and TV S' velocities ***(Al-Biltagi et al., 2015)***.

Diastolic dysfunction in fetuses of diabetic mothers often coexists with increased ventricular wall thickness, but may precede myocardial hypertrophy ***(Zielinsky et al., 2012)*** or be completely independent of its presence ***(Hatem, 2008).*** While IDMs in most studies of diastolic function have greater ventricular wall thickness than controls, altered filling patterns of mitral inflow Dopplers have been noted even without hypertrophy ***(Cimen, 2014)***.

Aim of the Work

To highlight subtle myocardial affection that might occur in asymptomatic infants of diabetic mothers which is not routinely detected by conventional echocardiographic scanning.

Chapter (1)

Infants of Diabetic Mothers

Diabetes mellitus:

In humans, normal glucose tolerance is maintained because of a balance between adequate insulin secretion and insulin sensitivity. The secretory response of the pancreatic b-cells to glucose (particularly in the early phase) and the sensitivity of the glucose utilizing tissues to insulin determine the ability of insulin to dispose carbohydrates ***(Baz et al., 2016)***.

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the pancreatic b-cells with consequent insulin deficiency to abnormalities that result in resistance to insulin action ***(American Diabetes Association, 2014).***

Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of uncontrolled diabetes

are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome. Long-term complications of diabetes include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes ***(American Diabetes Association, 2014).***

White`s classification of diabetes mellitus:

A: Abnormal glucose tolerance test at any age or of any duration treated only by diet therapy

- **A1**: Controlled by diet and exercise
- **A2**: Requires insulin

B: Onset at age 20 years or older and duration of less than 10 years.

C: Onset at age 10 to 19 years or duration of 10 to 19 years

D: Onset before 10 years of age, duration over 20 years, benign retinopathy, or hypertension (not preeclampsia).

- **D1**: Onset before age 10 years
- **D2**: Duration over 20 years

- **D3**: Calcification of vessels of the leg (macrovascular disease)
- **D4**: Benign retinopathy (microvascular disease)
- **D4:** Hypertension (not preeclampsia)

R: Proliferative retinopathy or vitreous hemorrhage

F: Renal nephropathy with over 500 mg/d proteinuria

RF: Criteria for both classes R and F

G: Many pregnancy failures

H: Evidence of arteriosclerotic heart disease

T: Prior renal transplant Gestational diabetes

(Bird et al., 2008)

Gestational diabetes mellitus (GDM):

GDM is defined as a glucose intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy ***(Fonseca, 2009).***

Alterations in maternal physiology during pregnancy are mediated by placental factors, as evidenced by the significant increase in maternal insulin sensitivity that occurs within days after delivery ***(Baz et al., 2016).***

Alterations in maternal metabolism have generally been ascribed to placental hormones, such as human placental lactogen (HPL), progesterone and oestrogen. Prolactin,

progesterone and estrogens also increase during pregnancy ***(Guyton and Hall, 2006)***.

The lipolytic effect of HPL allows the re-orientation of maternal metabolism toward lipid rather than glucose utilization, favoring glucose sparing for the fetus. The consequent increase in free fatty acid levels may participate to insulin sensitivity changes occurring during pregnancy as is the case in non-pregnant subjects. However, a direct effect of HPL on mother insulin sensitivity has not been demonstrated ***(Yoshino et al., 2014)***.

In addition, changes in inflammatory circulating factors such as tumor necrosis factor alpha (TNFa) may also be involved in pregnancy-associated insulin resistance, Meanwhile insulin secretion increases as a consequence to the development of insulin resistance ***(Friedman et al., 2008).***

Glycemic threshold for birth defects:

Periconceptional HgA1c is used as a surrogate marker for glycemic control and is almost linearly related to PGD-induced birth defects. Previous studies have shown that glucose control prior to or at early pregnancy, during organogenesis, can significantly reduce the incidence of birth defects ***(Galindo et al., 2006).***

Studies showed that when higher levels of HgA1c were evaluated (HgA1c greater than 10.1% - equal to 8 SD above the normal mean control value), there was statistically significant

higher occurrence rate of congenital malformation ($P < 0.01$) ***(Gabbay-Benziv et al., 2015).***

On the other hand it is difficult to differentiate PGD-induced anomalies from others encountered in nondiabetic pregnancies. Most studies use HgA1c to reflect the level of glycemic control, but HgA1c only measures a woman's average glycemic control over a 3-m period. Therefore, it does not necessarily reflect a woman's level of glycemic control during organogenesis and embryogenesis. Moreover, because it is an average measurement, the same level of HgA1c may reflect completely different glycemic patterns, one being constant around the average, and the other with larger fluctuations lower and above from the mean HgA1c value ***(Todorova et al., 2005)***. The effects of such fluctuations (i.e., episodes of acute hyperglycemia and hypoglycemia with "normal" HgA1c) are yet to be determined, in addition, the complicated metabolic nature of diabetes, coupled with metabolic changes that are normal during pregnancy, other factors may influence the developing embryo. Finally, lower prenatal detection rates of fetal anomalies (due to obesity, lack of prenatal care, etc.) in diabetic women may lead to statistic skewing when studying infants with congenital anomalies born to pregestational diabetic mothers PGDM ***(Dashe et al., 2009).***

Expected complications in infants of diabetic mothers:

1) Diabetic embryopathy / congenital malformations:

Worldwide, an estimated 8 million babies born to diabetic mothers, or 6% of all births, are complicated by congenital defects when followed up to early school age. About half of them are detected immediately after birth ***(Christianson, 2006).***

In the offspring of women with PGDM, birth defects occur in 5–10% of all live births, and in 2010, 8000 babies were born in the United States with a diabetes induced birth defect ***(Correa et al., 2012).***

Major congenital malformations in infants of diabetic mothers account for more than one-half of all perinatal deaths. Diabetic embryopathy can affect any developing organ system, although neural tube defects and cardiovascular malformations are the most common and severe congenital anomalies associated with diabetic pregnancy ***(Ornoy et al., 2015).***

The genetic basis underlying diabetic embryopathy remains largely unknown and most mechanistic work has emphasized the role of non-genetic (metabolic) factors ***(Ornoy et al., 2015)***.

Similarly, transcription factors, such as hypoxia-inducible factor-1a (HIF-1a) or ncRNAs, may be degraded according to developmental stages or environmental factors ***(Salbaum et al., 2011)***. The spatial and temporal deposition and

removal of epigenetic modifications during normal embryogenesis is achieved by the combined action of initiators (e.g., nc-RNAs), readers, writers, erasers, or insulators that form boundaries between epigenetic domains ***(Shen, 2013)***.

Abnormal maternal/fetal fuel metabolism, including hyperglycemia, hyperketonemia, and disordered metabolism of arachidonic acid, myoinositol, and prostaglandin, as well as increased oxidative stress have been shown to be responsible for some of the changes in embryonic development. High glucose levels during critical periods of morphogenesis appear to be the major teratogen in diabetic pregnancy ***(Ornoy et al., 2015)***.

2) Unexplained fetal demise/Stillbirths:

Fetal demise in absence of obvious factors such as placental insufficiency, abruption, fetal growth restriction or oligohydramnios is declared 'unexplained.'

Reported incidence is 1%in pre-gestational diabetes and 0.54%, 0.36% and 0.18% in untreated and treated gestational diabetes and nondiabetic mothers, respectively ***(Lang et al., 2005).***

In a large retrospective study published in 2015, relative risk RR of stillbirth was 2.5 in type 2 and 1.4 in type 1 diabetes compared to non-diabetes ***(Jovanovi et al., 2015).***

These are typically macrosomic babies with fetal hyperinsulinemia as the possible cause of death. Fetal

hyperinsulinemia increases fetal metabolic rate and oxygen demand in fetus leading to chronic hypoxemia and lactic academia. Other risk factors include poor glycemic control which leads to villous edema and placental dysfunction, hence fetal hypoxia and acidosis.

Extramedullary hematopoiesis as evidenced by relative foetal erythraemia in cord blood supports chronic hypoxia as the cause of foetal death. Foetal hypertrophic cardiomyopathy, maternal diabetic vasculopathy, preeclampsia and ketoacidosis further contribute by reducing placental blood flow and fetal oxygenation are other contributing factors. Fetal demise occurs most often after 36 weeks of pregnancy, but can be seen as early as second trimester in women with vascular complications. Still births within 72 hours of seemingly normal fetal heart tracings have been reported ***(Kulshrestha and Agarwal, 2016).***

3) Intra-uterine growth restriction (IUGR):

Women with unexplained fetal growth restriction have greater maternal insulin sensitivity resulting in decreased nutrients available for placental transport to the fetus. This reinforces the need for frequent fetal surveillance ***(Landon, 2013).***

4) Low birth weight (LBW):

LBW in infants of mothers with PGDM is usually a sign of severe diabetic vascular complications and is observed in increasing frequencies in women with PGDM and hypertension, renal disease, or in malformed infants. The rate of LBW in women with GDM and mean gestational blood glucose levels below 87 mg was 20%, significantly higher than in controls that had only 11% of LBW infants ***(Ornoy et al., 2015).***

5) Preterm birth

A number of studies have reported an increased risk of preterm births in case of diabetes. However, data are not always available on the respective proportion of induced and spontaneous births, considering the increased maternal and fetal morbidity of diabetes during pregnancy ***(Mitanchez et al., 2015).***

The benefits of early delivery to avoid fetal death or shoulder dystocia must be balanced against the morbidity linked to preterm birth, especially the respiratory morbidity. The link between GDM and spontaneous preterm birth is still controversial ***(Mitanchez et al., 2015).***

6) Macrosomia:

Macrosomia is the most constant complication in GDM. The concept of excessive fetal growth is expressed either by the word "macrosomia" or by the expression "large for gestational age" (LGA). Macrosomia is defined by a birth weight (BW) of > 4 kgs. However, in this definition, gestational age (GA) is not taken into account. The term LGA corresponds to a BW ≥ 90th percentile or >2SD (<97th percentile) for GA. This definition allows premature newborns with excessive fetal growth to be identified. Macrosomia in newborns of diabetic mothers is characterized by excess body fat, an increased muscle mass and organomegaly, without increase in brain size ***(Mitanchez et al., 2015).***

Both gestational and pre-gestational diabetes mellitus are independent risk factors for macrosomia, which complicates 34% of gestational diabetes, 40% of pre-gestational type 1 and 2 diabetes compared to 9% in women with optimum glycemic control (i.e <110 mg/dL mean capillary glucose levels ***(Landon, 2013).***

Fetal overgrowth is related to increased transplacental transfer of maternal glucose, which stimulates the release of insulin by fetal pancreatic beta cells**.** Insulin is a major factor of fetal growth and it up-regulates the Insulin-like Growth Factor (IGF) system, subsequently leading to fetal macrosomia ***(Simeoni, 2009).***

The HAPO study (Hyperglycemia and adverse pregnancy outcomes study) showed a continuous, positive association between maternal glycemia, fetal hyperinsulinism and BW ***(Metzger et al., 2008).*** A linear and continuous relationship between body fat percentage in newborns, maternal glycaemia and fetal insulin levels has been found ***(HAPO Study Cooperative Research Group; 2009).***

More recently, other mechanisms that may also contribute to fetal overgrowth were evoked, like maternal metabolic environment and placental modifications ***(Vambergue, 2011).***

In particular, maternal lipids availability and transport to the fetus may be enhanced in case of maternal diabetes ***(Catalano, 2011).***

Macrosomic newborn infants can be categorized into 3 groups:

Grade 1 macrosomia:

Newborn infants who weigh 4000 to 4500 g: Delivery of macrocosmic fetus is associated with prolonged labour, an increased likelihood of operative delivery, shoulder dystocia, clavicular fractures, and brachial plexus injury that may be permanent ***(Kulshrestha and Agarwal, 2016).***

Grade 2 macrosomia:

Newborns with weights between 4500 and 4999 g: In addition to the above complications, these are further at significant risk for neonatal morbidity including perinatal asphyxia, 5-minute Apgar score of <3, assisted ventilation, meconium aspiration, and hyaline membrane disease ***(Kulshrestha and Agarwal, 2016).***

Grade 3 macrosomia:

Defined as a birth weight of > 5000 grams: These have increased infant mortality rates compared to grade 1 and 2 macrosomia ***(Kulshrestha and Agarwal, 2016).***

7) Metabolic disorders

Hypoglycemia:

The link between macrosomia, increased cord C-peptide levels that reflects fetal insulin secretion, and neonatal hypoglycemia has long been known. The infant of a diabetic mother is at risk of transient hyperinsulinism, which prevents at birth the normal activation of metabolic pathways producing glucose and ketone bodies, and causes increased glucose consumption by tissues ***(Hawdon, 2011)***.

The exact incidence of hypoglycemia in case of maternal diabetes is difficult to assess due to the various definitions used for neonatal hypoglycemia in the literature ***(Mitanchez et al., 2015).***