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Clinical significance of DVM and its prevalence in pre-gestational diabetes cases versus normal pregnancies

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ABSTRACT

Pre-gestational diabetes mellitus affects less than 1% of all pregnancies and is a significant cause of fetal morbidity and mortality. It is hypothesized that impaired placental function, in the form of abnormal placental weight and/or abnormal placental histology, may be responsible for this event in such pregnancies. Delayed villous maturation of placental villi, which is one of the findings associated with pre-gestational diabetes increases the rate of perinatal mortality. There is limited literature regarding the delayed maturation of placental villous. This review included trials (randomized and non-randomized), cohort and case-control studies registered in Medline/PubMed database, from January 2001 to September 2012 that evaluated the clinical significance of delayed villous maturation and its prevalence in pre-gestational diabetic cases compared to normal pregnancies.
It emphasizes that further studies with focus on possible clinical or ultrasound markers of placental delayed villous maturation, especially in a high risk-group such as women with pre-gestational diabetes mellitus are highly recommended.

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Introduction

Diabetes mellitus is a relatively common condition in pregnancy, affecting up to 7% of the pregnant population (1). Perinatal morbidity and mortality increase in infants of mothers with diabetes mellitus (2). Pre-gestational diabetes mellitus (PGDM) affects less than 1% of all pregnancies and is a significant cause of fetal morbidity and mortality (3). Even in controlled pre-gestational diabetic mothers, the risk of perinatal mortality increases due to fetal cardiomyopathy and late third trimester unexplained etiologies (4-6).

In general, chronic hypoxia, hyperglycemia and lactic acidosis result in increased intrauterine death; however, it is hypothesized that in such pregnancies impaired placental function, in terms of abnormal placental weight and/or abnormal placental histology, may account for this phenomenon (7).

The placental which is an essential link between the mother and fetus has a significant role in fetal development mainly by gaseous exchange, provision of nutrients, hormonal excretion and maternal antibodies transmission (8).

Placental implantation abnormalities and intrinsic diseases result in many pregnancy complications including pre-eclampsia, intrauterine growth restriction, fetal hypoxemia and sudden intrauterine death (3,9). On the other hand, delayed maturation of placental villous, which is one of the findings associated with pre-gestational diabetes, increases the rate of perinatal mortality (10,11).

Delayed villous maturation (DVM) is a spectrum of placental disease characterized by decreased

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tertiary villous formation, reduced vasculosyncytial membrane formation and increased large bullous villi in its more severe forms. In some studies, it has been associated with an increased risk of stillbirth in the late third trimester, but in general few data are available on its significance (10).

Therefore, the delayed maturation of placental villi might be the main etiology for the increased risk of intrauterine death in certain cases. There are limited literature regarding the delayed maturation of placental villous; however, few studies have investigated the association between maternal diabetes and the villous immaturity (12,13). This study is a review of the clinical significance of DVM and its prevalence in normal pregnancies in comparison to pre-gestational diabetic cases.

Literature review

This review included trials (randomized and non-randomized), cohort and case-control studies registered in Medline/PubMed database, from January 2001 to September 2012 that evaluated the clinical significance of delayed villous maturation and its prevalence in pre-gestational diabetic cases compared to normal pregnancies.

In the study by Higgins et al. in 2011, 175 DVM cases were compared with 175 controls matched for gestation and delivering within the same time period. In this study, DVM was significantly associated with pre-gestational diabetes (8% vs. 2.8%, P <0.05) and prenatal or intrapartum intrauterine death (8.6% vs. 0%, P <0.05). Infants with the diagnosis of DVM had a statistically higher birth weight and were more likely to require special care baby unit admission (10).

Stallmach et al. investigated the impact of the pattern of placental dysfunction on the risk of recurrent stillbirth or maternal disease in later life on a population survey of 17,415 consecutive unselected singleton placentas. Eleven percent of mothers with placental maturation defects had diabetes in the index pregnancy; none of the other women in this group developed diabetes over the 5 to 20-year observation period. In this survey, incidence of maturation defect was 5.7%, which was associated with fetal death in 2.3% of cases. Normal placentas were associated with fetal death in 0.033% of cases (14).

In 2008, Russell et al. studied stillborn infants of mothers with diabetes mellitus in comparison to appropriately grown stillborn nondiabetic infants when adjusted for birth weight. The first group had heavier hearts, thicker ventricular free wall measurements and lighter brains. Cardiomegaly was reported in 22% of stillborn LGA (large for gestational age) infants while stillborn appropriately grown infants showed no difference in heart weights corrected for birth weight (4).

In Evers et al. study, histological abnormalities such as the presence of nucleated fetal red blood cells, fibrinoid necrosis, villous immaturity and chorangiosis were observed more frequently in the diabetic placenta rather than the control placenta. They concluded that placenta of women with type 1 diabetes showed several abnormalities that could be with the cause of impaired functioning (7).

Higgins et al. in 2012, studied 77 non-diabetic women and 74 PGDM cases to prospectively compare the incidence of DVM in PGDM population with non-diabetic controls. In the mentioned study, DVM had a higher incidence in the PGDM group compared to the non-diabetic group (p=0.02). However, no difference in perinatal outcome nor in glycemic control was observed between the two groups. The incidence of a placental diagnosis of DVM amongst the women with PGDM, was 28.4% compared to 14.3% in the control group. Thus, the incidence of DVM in the PGDM cohort was almost twice that of controls. Maternal diabetes was the most significant factor in prediction of placental DVM (p=0.01) with infant's gender stood last in the exclusion list. No difference in mean HbA1c or fructosamine was recorded between pre-gestational diabetic mothers with or without placental DVM at any gestational age (3).

Regarding clinical outcome within the PGDM group itself, except for an increased birth weight in the DVM group, no other clinical outcomes differed between those with a placental diagnosis of DVM and those without.

In the study by Evers et al. the incidence of fetal macrosomia in a non-selected nationwide cohort of 289 women with Type 1 diabetes mellitus was investigated. Despite apparent good glycaemic control, the incidence of fetal macrosomia was still very high. They referred to the third trimester HbA (1c) as the most powerful predictor, but with a weak predictive capacity (15).

It is worth noting that haemoglobin oxygen affinity is increased in diabetic women compared to non-diabetic controls in late pregnancy and this increased affinity is in direct proportion to increases in HbA1c. Therefore it is possible that poorer glycaemic control would result in the increased incidence of DVM and worsen its effects (3).

In 1976, the morphologic characteristics of the chorial villi from normal full-term placentas were compared with placentas of different clinical types of diabetic women. The latter showed early maturation of the trophoblast, higher percentage of villi with stromal edema, and higher percentage of vessels of the villous trunks with lesions causing partial or total obstruction of the vascular lumen (16).

DVM, in which tertiary villi are less mature than

what is expected for the gestational age of the placenta is linked with an increased risk of perinatal mortality and is more commonly seen in the PGDM population compared to non-diabetic mothers. Delayed villous maturation is associated with both gestational diabetes mellitus, pregestational diabetes mellitus and with perinatal death (3,10).

In a recent study by Higgins et al., no association was found between DVM occurrence and maternal glycemic control. The presence of placental DVM was not associated with antenatal ultrasound parameters nor clinical perinatal outcome (3).

In another study examining the stereological aspects of pre-gestational diabetic mothers` placenta showed that maternal glycemia has influenced capillary, but not stromal or the development of the placental. This suggested that other factors besides glycaemia are involved in placental development in pre-gestational diabetes (10).

Stallmach et al. in 2001, stated that placental maturation defect can be a cause of fetal hypoxia. In this study, although the risk of stillbirth was 70 times greater than that of a normal placenta, a few affected fetuses actually died. They reported the risk of recurrent stillbirth to be tenfold above the baseline and to mostly occur after 35 weeks' gestation (14).

On the other hand, cardiomyopathy and cardiomegaly are a common finding in stillborn infants of diabetic mothers and may contribute to the risk of fetal death in these pregnancies by progression towards congestive heart failure (15).

Jacombo et al. concluded that metabolic correction of diabetes mellitus prevents the occurrence or the development of the multiple disturbances during pregnancy (16).

It is worth noting that though it has been reported that diabetes almost doubles the risk of DVM, there is still a 14% baseline risk of DVM in the low risk nondiabetic normal obstetric population (3).

Conclusion

Today, delayed villous maturation remains a clinically important concern in women with pregestational diabetes due to its proven connection with perinatal mortality and higher rate of intrauterine death; whereas its adverse effects on fetal wellbeing cannot be detected by currently used methods such as Apgar scores or cord pH.

Recognition of DVM may assist in explaining the loss of term infants in some cases by consideration of earlier delivery, thus resulting in "rescue by birth."

Eventually, future studies which focus on possible clinical or ultrasound markers of placental DVM are highly recommended, especially in a high risk-group such as women with PGDM.

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Conflict of Interest

The authors declare no conflict of interest.

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