Dimitrios Siassakos*, Isabella Bourne, Neil Sebire, Lindsay Kindinger, Sara Melissa Whitten and Clarissa Battaglino

Abnormal placental villous maturity and dysregulated glucose metabolism: implications for stillbirth prevention

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Abstract

Objectives: In the UK one in 250 pregnancies end in stillbirth. Abnormal placental villous maturation, commonly associated with gestational diabetes, is a risk factor for stillbirth. Histopathology reports of placental distal villous immaturity (DVI) are reported disproportionately in placentas from otherwise unexplained stillbirths in women without formal diagnosis of diabetes but with either clinical characteristics or risk factors for diabetes. This study aims to establish maternal factors associated with DVI in relation to stillbirth.

Methods: Placental histopathology reports were reviewed for all pregnant women delivering at University College London Hospital between July 2018 to March 2020. Maternal characteristics and birth outcomes of those with DVI were compared to those with other placental lesions or abnormal villous maturation.

Results: Of the 752 placental histopathology reports reviewed, 11 (1.5%) were reported as diagnostic of DVI. Eighty cases were sampled for clinical record analysis. All women with DVI had normal PAPP-A (>0.4 MoM), normal uterine artery Doppler studies (UtA-PI) and were normotensive throughout pregnancy. Nearly one in five babies (2/11, 18.5%) with DVI were stillborn and 70% had at least one high glucose test result in pregnancy despite no formal diagnosis of diabetes.

Conclusions: These findings suggest that the mechanism underlying stillbirth in DVI likely relates to glucose dysmetabolism, not sufficient for diagnosis using current criteria for gestational diabetes, resulting in placental dysfunction that is not identifiable before the third trimester. Relying on conventional diabetes tests, foetal macrosomia or growth restriction, may not identify all pregnancies at risk of adverse outcomes from glucose dysmetabolism.

Keywords: accelerated villous maturation; distal villous immaturity; foetal vascular malperfusion; gestational diabetes; maternal vascular malperfusion; stillbirth; stillbirth prevention; villous dysmaturity.

Introduction

Around one in 250 births end in stillbirth in the UK [1]. Gestational diabetes mellitus (GDM) is a risk factor for stillbirth [2] and its prevalence is increasing alongside rising rates of obesity, type 2 diabetes mellitus and advanced maternal age [3, 4]. The potentially lethal consequences of undiagnosed gestational diabetes are well established; women with raised fasting plasma glucose (FPG) levels not diagnosed with GDM have a four-fold increased risk of stillbirth compared to women with normal FPG values (aOR 4.22, 95% CI 1.04–17.02), and to those with a formal diagnosis of GDM (aOR 1.10, 95% CI 0.31–3.91) [5].

Historically, there has been global variation in glucose tolerance test (GTT) diagnostic criteria. In HAPO, 14.3% of women had GDM by three-step IADPSG criteria but not two-step criteria [6]. Studies have shown that women who met IADPSG three-step criteria but who were not diagnosed with GDM based on two-step (e.g. NICE) diagnostic strategies [4], and were therefore not treated, had an increased risk for adverse perinatal outcomes compared with women
Materials and methods

This was a retrospective case control study investigating clinical factors relating to DVI. Ethics Committee approval was not required as the data were collected as part of the service and no identifiable data were included.

We reviewed all 752 placental histopathology reports and pregnancy outcomes for women delivering at University College London Hospital (UCLH) who had placentas submitted for histological examination between July 2018 and March 2020.

Any histopathology report with mention of AVM or DVH was included in the dataset. Any other abnormalities associated with AVM, MVM and FVM were also included. These included descriptions of small straight villi, hypoplastic villi, villous oedema, avascular villi, fibrin thrombi, intervillous thrombus, inter villous or perivillous fibrin deposition, increase in syncytial knot formation, areas of infarction, a macroscopically small placenta. Cases with foetal abnormality, villitis or chorioamnionitis alone were excluded.

We identified 237 cases of abnormal placental villous histology. Lesions were grouped into categories (Table 1) compliant with the Amsterdam Placental Workshop Group Consensus Statement [10] but with effort to isolate abnormalities relevant to glucose dysmetabolism alone from those associated with pre-eclampsia superimposed on gestational diabetes.

Clinical records were accessed on Epic™ and ViewPoint™ electronic health record databases through linkage of hospital number or name and date of birth. All patients according to the local protocol had a random blood glucose (BG) in the first trimester, a glucose challenge test (GCT) in the late second trimester and a third trimester 2 h GTT with 75 g dependent on risk factors. Women with foetal macrosomia had home blood glucose monitoring (HBGM).

For the purpose of this study, we considered borderline high values for glucose testing to be ‘abnormal’: indicative of potential glucose dysmetabolism. Booking glucose was considered ‘abnormal’ at >5.0 mmol/L, and >7.0 mmol/L was the threshold for GCT. GTT values were considered to be high if 60 min BG was >10 mmol/L and 120 min BG was >7.0 mmol/L. Risk factors for diabetes evaluated in the clinical records were maternal age >40 years, BMI >30, pre-pregnancy polycystic ovary syndrome (PCOS), a first degree relative with diabetes, previous macrosomic baby or previous stillbirth.

Maternal demographics and pregnancy outcomes were recorded, including maternal comorbidities, gestational diabetes, hypertensive disease, antenatal scan findings and birth outcomes. Maternal characteristics and pregnancy outcomes were compared between groups using Fisher’s exact test (Figure 1).

Results

A total of 80 cases were included in the study. Indications for histopathology varied; groups and ranged from obstetric history (adverse outcome, molar pregnancy) to unexpected poor neonatal condition. Group A included placental histopathology with abnormal villous maturation (n=23) and was separated into A1, AVM or villous hypoplasia (n=12) and A2, DVII (n=11). So that all groups would have similar number of cases, the 23 cases of villous
maturation were matched to 18 cases (group B), 20 cases (group C) and 19 cases (group D) for clinical record analysis.

Group B (n=18) included cases with abnormal villous histology but with no direct mention of delayed or accelerated maturation. Two cases were excluded as there was coexistent villous oedema and severe chorioamnionitis. This group was further split into two groups; B1 (n=11) included cases with FVM and descriptions of segmental avascular villi or thrombosis. B2 (n=7) included reports of villous oedema, a non-specific finding.

Cases in group C (n=20) show a combination of features of both abnormal villous maturation and MVM. That is, mention of either A or B lesions plus a mention MVM or findings associated with MVM such as increased syncytiotrophoblastic knot formation, intervillous thrombus, infarction, perivillous fibrin or fibrin thrombi.

Group D (n=19) includes findings suggestive of MVM but no factors mentioned suggestive of otherwise abnormal villous maturation.

There were no cases of pre-existing diabetes. PCOS was found only in cases with MVM (groups C and D) in this study. Advanced maternal age >40 and hypertensive conditions were most prevalent in groups A1, C and D compared to group A2 and B1 (Table 1). DVI (group A2) was associated with numerically higher rates of stillbirth (n=2/11, 18.2%) and maternal BMI >30 (n=2/10, 20%), compared to other groups (Table 2). None of the mothers to babies that were stillborn with DVI were >40 years old, none had pre-existing diabetes, none had chronic hypertension (Table 1).

All (100%) women with DVI and FVM had normal first trimester pregnancy associated plasma protein-A (PAPP-A) levels (>0.4 MoM), a proportion significantly higher for DVI and FVM than all other groups. All (100%) women with DVI had normal uterine artery Doppler studies, a proportion significantly higher for DVI than all other groups. In contrast, 55.6% (5/9) of the women with FVM (another histopathology possibly associated with undiagnosed diabetes) had abnormal uterine artery Doppler pulsatility index (PI) by UCLH criteria (total bilateral >2.5). No woman with DVI had pregnancy induced hypertension.

A total of 63.2% (12/19) of those with combined abnormal villous maturation and MVM (group C) showed pre-eclampsia and 73.7% (14/19) had FGR, whereas those with MVM alone (group D) showed 29.4% (5/17) and 33.3% (5/15) of pre-eclampsia and FGR respectively.

Of those with AVM (A1) and DVI (A2), 83% (10/12) and 80% (8/10) respectively had at least one abnormal glucose test result or risk factor for diabetes. Substantially more women with disorders of villous maturation had at least one abnormal glucose test result (random glucose or GCT) compared to other groups (70%, 7/10, in group A2 vs. 28.6%, 41.2%, 27.8% in groups B2, C, D respectively), despite no formal diagnosis of diabetes (normal GTT/HMG). Of the seven women with DVI (A2) with an
formal diagnosis of GDM

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\text{PI} > 2.5^a
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(A1 = Accelerated maturation (n=12)

A2 = Distal villous immaturity (n=11)

B1 = FVM (n=11)

B2 = Villous oedema (n=7)

C Combined dysmaturity (n=20)

D MVM alone (n=19)

Denominators reflect unavailable data (e.g. PAPP-A not performed). GDM, gestational diabetes mellitus; PET, pre-eclampsia; FGR, foetal growth restriction; FVM, foetal vascular malperfusion; MVM, maternal vascular malperfusion. $^a$ p<0.001 A2 vs. other groups, $^c$ p<0.05 A2 and B vs. other groups.

**Discussion**

The results suggest that women with abnormal villous maturation and diabetes, particularly those with FVM, are at increased risk of adverse outcomes. This was supported by a retrospective review of clinical reports, indicating that the reporting pathologists were not blinded to the clinical history. Further, women with diabetes and screening for placental dysfunction may be underdetected using current criteria for detection of placental histopathology.

Women with dysregulated placental metabolism may have abnormal uterine artery PI despite normal 1st 24 h GTT. This was associated with significantly higher rates of macrosomia than all other groups (36% vs. 9%, 5%, 6% and 0% in groups A1, B1, C and D, respectively). Half (50%) of their babies were normal weight, 310 had macrosomia, and 210 were growth restricted.

Abnormal glucose test result (3/7 had an abnormal GTT, 2/7 had a normal GTT), DVI was also associated with significantly higher rates of macrosomia than all other groups (36% vs. 9%, 5%, 6% and 0% in groups A1, B1, C and D, respectively). Half (50%) of their babies were normal weight, 310 had macrosomia, and 210 were growth restricted.
insufficiency including advanced maternal age >40 years and hypertensive disease, were not prevalent in the DVI group. There appears to be much higher levels of pre-eclampsia and foetal growth restriction when both abnormal villous maturation and MVM (group C) placental lesions are present, compared to MVM alone (group D).

Our analysis of placental pathology in association with maternal characteristics and birth outcomes enables us to broadly categorise women two categories; those with placental dysfunction primarily related impaired placentation and MVM and those with dysfunction primarily related to abnormal maturation and glucose metabolism. Since diabetes mellitus may also be associated with pre-eclampsia, placentas may have features of more than one histopathological pattern, making sufficiently powered research difficult. FVM appears to be an example of complex underlying pathophysiology and may in part result from multiple different insults leading to signs of FVM in stillbirths, such as viral infections and umbilical cord variations [15], or mild thrombophilias, particularly when combined with undiagnosed diabetes affecting red cell deformability. The potentially severe consequences of fetal vascular malperfusion have recently been highlighted by Gardella et al. including an increased risk of severe neurodevelopmental impairment at two years of age in pregnancies complicated by early (<34 weeks) fetal growth restriction [16]. Yet, the relative contribution of glucose dysmetabolism, umbilical cord abnormalities and other pathologies to the pathogenesis of FVM remains unknown.

Diabetes mellitus represents a disease spectrum [7] and the study results suggest that relying on conventional diabetes tests, fetal macrosomia or growth restriction may not identify all pregnancies at risk of stillbirth from glucose dysmetabolism. Moreover, models of stillbirth prevention focussing on PAPP-A and uterine artery PI, as well as maternal age, considered to be amongst the best prognostic markers alongside placental growth factor (PlGF) [17] might miss every single case at risk of DVI. Prevention of harm could instead involve testing for dysmetabolism with more sensitive criteria, and novel approaches including antenatal micro-imaging of the placenta. The human placenta project strives to develop new technologies for the real-time assessment of placental development and interventions to prevent abnormal placental development [18].

The need for progress is urgent. Whilst otherwise ‘unexplained’ stillbirths may occur in women with markers of diabetes associated with placental DVI or FVM, identification and treatment of glucose dysmetabolism with carbohydrate restriction and if necessary, insulin may reduce both the incidence and the severity of FVM [19]. It remains uncertain whether early diagnosis and treatment might ameliorate DVI progression. In the meantime, all women in pregnancy should be supported and encouraged to have a healthy lifestyle including exercise [20].

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