Placental disease and abnormal umbilical artery Doppler waveforms in trisomy 21 pregnancy: A case-control study

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ABSTRACT

Introduction: The objectives of this study were firstly to determine the proportion of placental pathology in fetuses affected by trisomy 21 (T21) using current pathological descriptive terminology and secondly to examine if a correlation existed between the finding of an abnormal umbilical artery Doppler (UAD) waveform, the presence of T21 and defined placental pathological categories.
Methods: This case-control study assessed singleton fetuses with karyotypically confirmed trisomy 21 where placental histopathology had been conducted from 2003 to 2015 inclusive, within a university tertiary obstetric centre. This was compared with unselected normal singleton control pregnancies matched within a week of gestation at delivery. Data included birthweight centiles and placental histopathology. Comparisons of Doppler findings across placental pathological categories were performed using statistical analysis.
Results: 104 cases were analysed; 52 cases of trisomy 21 and 52 controls. Fetal vascular malperfusion (48.1% vs. 5.8%, p = 0.001) and maturation defects (39.2% vs. 15.7%, p = 0.023) were more common in trisomy 21 placentas. Compared with controls, trisomy 21 fetuses were more likely to have shorter umbilical cords (p = 0.001) and had more UAD abnormalities. Amongst T21 pregnancies, umbilical artery Doppler abnormalities are associated with the presence of maternal vascular malperfusion.
Discussion: Fetal vascular malperfusion and maturation defects are more common in trisomy 21 placentas. Abnormal umbilical artery Doppler waveforms are more common in T21 and are associated with maternal vascular malperfusion. Placental disease may explain the increased rate of intrauterine death in T21.

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1. Introduction

The incidence of T21 rises with increasing maternal age [1] and the introduction of NIPT has facilitated its early recognition. The incidence of live-born T21 neonates is on average 10.2 per 10,000 live births [2], but varies between countries; with rates in Ireland, Malta and Poland almost double that of the UK. This may be in part explained by differing termination of pregnancy practices. Fetuses with T21 are more likely than euploid fetuses to die in utero [3]. Recent research suggests that rates of live-born T21 babies have remained stable or slightly increased in the United States and the Netherlands, supporting the need to understand the underlying pathology in such pregnancies and utilise such information to tailor obstetric management. With a trend towards advancing maternal age, the proportion of fetuses with T21 is expected to rise, and although NIPT will detect many of these, a significant number will continue to term. Hence, it is important to be aware of the antenatal

management of a pregnancy affected with a T21 fetus [3–5].

Whilst it is commonly accepted that T21 fetuses are more likely to exhibit an abnormal UAD waveform, the evidence for this is scant [6,7]. The UAD assesses the direction, velocity and volume of blood in the umbilical artery. Abnormal waveforms, including elevated PI and AEDF/REDF are associated with adverse fetal outcome [8]. The UAD acts as an assessment of impedance within the feto-placental circulation, an abnormal waveform suggesting the presence of increased placental vascular resistance. It is a tool commonly used to screen for and to assess fetal growth restriction [9]. However, there is relatively little in the literature that examines placental findings in T21, using recently agreed placental terminology, and that relates this to UAD findings [10].

Obstetricians may be faced with the challenging situation of a T21 fetus with an abnormal UAD. This poses a dilemma with regards to aggressive versus non-aggressive management, such as preterm delivery of a fetus that may have underlying congenital anomalies [11]. This makes the timing of delivery and the significance of such Doppler findings a challenge as it may or may not co-exist with placental insufficiency or fetal growth restriction [7].

The objectives of this study were to firstly determine the proportion of placental pathology in fetuses affected by T21 using current pathological descriptive terminology and secondly to examine if there is a correlation between the finding of an abnormal UAD waveform, the presence of T21 and defined placental pathological categories.

2. Methods

This retrospective case control study was performed between 2003 and 2015 inclusive in the Department of Pathology and Laboratory Medicine in the National Maternity Hospital, Dublin, Ireland. This tertiary maternity hospital delivers 9500 babies per annum. A triage system ensures examination of placentas where there is a relevant clinical or gross pathological indication.

All placentas of singleton fetuses with a post-natally confirmed karyotype of T21 delivered in this centre above 24-completed week's gestation were included in this analysis. Cases included live births and stillbirths. Fetuses where complete histopathological analysis was not performed, or where mosaicism was present, were excluded. The control group included singleton fetuses without known aneuploidy matched within a week of gestation at delivery, and where placental histopathology had been performed. Exclusion criteria for controls were congenital anomaly, SGA, early onset pre-eclampsia (≤34 weeks gestation), pregnancy-induced hypertension and stillbirth or neonatal death.

Outcome measures collected included maternal demographics, the co-existence of a structural anomaly, birth weight centiles (SGA was defined as a customised birth weight <10th centile), fetal/neonatal outcome and umbilical artery Doppler findings (normal, elevated umbilical artery Doppler PI and AEDF/REDF).

The placenta was sampled to include cord, membranes and parenchyma. Grossly visible lesions were sampled (excluding peripheral infarcts <5% at term). In each case, at least two full-thickness samples of the inner 2/3 of the disc were included.

Placental pathology was defined as follows: (i) MVM was used in preference to maternal vascular underperfusion, reflecting recent consensus terminology [12]. Lesions included syncytial knots present in ≥33% of villi, accelerated villous maturation (defined as the presence of small or short hyper-mature villi for gestational age) and distal villous hypoplasia (defined as the paucity of terminal villi in relation to surrounding stem villi). Placentas with infarction >5%, retroplacental haemorrhage and decidual arteriopathy were also included in the MVM category. (ii) FVM was used, reflecting recent consensus terminology. This was diagnosed as high-grade if there

was more than one focus of avascular villi (cumulatively >45 over three sections or >15 villi per section) with or without thrombus, or two or more occlusive or non-occlusive thrombi in the chorionic plate or major stem villi, or multiple non-occlusive thrombi. Findings less than these were classified as low-grade [12] (iii) Villitis - defined as infiltration of villi by lymphocytes and/or histiocytes and graded as high or low-grade according to the criteria of Redline [13] (iv) Acute inflammation: maternal acute inflammation was identified by the presence of polymorphs and graded by their presence in the chorion only (stage 1); extension to the amnion (stage 2) and necrotising chorioamnionitis (stage 3) (v) For placental maturation, the term delayed villous maturation was used, reflecting recent consensus terminology [12]. It was diagnosed after 34 completed weeks of gestation where there was a monotonous population of villi with reduced vasculosyncytial membranes for gestation, usually accompanied by a continuous cytotrophoblast layer and centrally placed capillaries. (vi) Cord hypercoiling was defined as an umbilical coiling index of ≥0.3 and hypocoiling as ≤0.1.

Placental histopathology was performed by two experienced placental pathologists (EEM and PD). Ultrasonography was performed in the Department of Fetal Medicine by trained sonographers using a Voluson®ultrasound system (GE Healthcare 2003–2014). Outcome data was obtained from: (i) a computerised patient detail ultrasound recording system (Viewpoint® Version 6, GE Healthcare, UK) and (ii) a computerised patient note system (PAS®).

Statistical analysis was performed by a biostatistician (RS) using IBM® SPSS v20®. Due to the paired nature of the case-control sample, non-dependent group tests were used throughout, including the paired *t*-test or Wilcoxon signed rank test for continuous risk factors, and the McNemar-Bowker test for categorical factors. The case-only analyses used Pearson's chi-square tests to compare UAD with placental pathology categories. Statistical significance was set at 0.05.

3. Results

3.1. Demographics

One hundred and four cases were included; 52 cases of T21 and 52 controls. The demographics of the study population are outlined in Table 1. Mothers of infants with T21 were older, although not significantly so (p = 0.07). Due to case selection, there were significantly more stillbirths (n = 18) and NNDs (n = 1) in the T21 group (p = 0.001). The proportion of SGA babies (<10th centile) was higher (p = 0.001) (Where assessed (n = 47)). There were significantly more fetuses with an abnormal umbilical artery Doppler waveform in the T21 group (Table 2).

3.2. Congenital anomalies

There were significantly more infants with structural anomalies in the T21 cohort diagnosed both ante-natally and post-natally (cases n = 34, 65.4% vs. controls n = 1, 1.9% p = 0.001). Cardiac and digestive system anomalies were most frequent, with rates of 36.5% and 19.2% respectively. In cases diagnosed ante-natally defects included duodenal atresia n = 3, non-immune fetal hydrops n = 3, atrial-ventricular septal defect n = 2 and ventriculomegaly n = 1. In the cases of stillbirths/neonatal deaths, a post-mortem was performed in 14/19 (73.7%). Cases with underlying causes/co-existing anomalies including hypoxic ischemic encephalopathy n = 5, duodenal atresia n = 3, ventricular-septal defect n = 3, severe fetal growth restriction n = 2 and abnormal myelopoesis n = 1.

Cardiac anomalies were more common overall in cases with abnormal and reversed end diastolic flow (4/5, 80%). These were