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Fetal thrombotic vasculopathy is associated with thromboembolic events and adverse perinatal outcome but not with neurologic complications: A retrospective cohort study of 54 cases with a 3-year follow-up of children

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ABSTRACT

Objective: to test the hypothesis that placental fetal thrombotic vasculopathy (FTV) is associated with obstetric complications and predisposes the child to unfavorable outcomes.
Methods: 54 placentas with FTV lesions and 100 placentas without FTV lesions were collected over a 5-year period at the Croix-Rousse Pathology Department. Clinical findings including maternal, fetal, neonatal condition and pediatric outcome up to three years were collected for each case and control observation. The statistical analyses were assessed with Wald's chi-square derived from conditional logistic regression modeling.
Results: FTV was associated with a significantly higher frequency of obstetric complications: (pregnancy-induced hypertension (OR 3.620, CI 1.563–8.385), preeclampsia (OR 3.674, CI 1.500-8.998), emergency delivery procedures (OR 3.727, CI 1.477–9.403), cesarean sections (OR 2.684, CI 1.016–7.088)), poor fetal condition (intrauterine growth restriction (IUGR) (OR 5.440, CI 2.007–14.748), nonreassuring fetal heart tracing (OR 6.062, CI 2.280–16.115), difficulties in immediate ex utero adaptation (OR 3.416, CI 1.087–10.732)) and perinatal or early childhood demise (OR 3.043, CI 1.327–6.978). On pathological examination, FTV was associated with marginal cord insertion (OR 3.492, CI 1.350–9.035), cord stricture and hypercoiled cord (OR 3.936, CI 1.209–12.813). Thromboembolic events were significantly more frequent in cases with FTV (OR 2.154, CI 1.032–5.622). Neurological complications within the first 3 years of life were also more frequent in the FTV group compared to the control group, but this association was not statistically significant.
Conclusions: FTV is associated with maternal complications, pathological findings in the placenta, especially gross cord abnormalities, IUGR, and poor perinatal or early childhood outcome. It may also predispose children to somatic thromboembolic events.

1. Introduction

Fetal thrombotic vasculopathy (FTV) is a recently described disease [1,2] related to obliteration of the fetal vascular flow. On histological examination, it is defined by the presence of avascular terminal villi, fetal vessel thrombosis, endothelial cushions (or intimal fibrin cushion), hemorrhagic endovasculitis, and according to some authors, fibromuscular sclerosis [2,3].

This rare disease has a frequency varying from 0.3 to 6.4% [1,4]. Its clinical features are not well known. It can remain asymptomatic at birth, induce intrauterine growth restriction (IUGR), or cause intrauterine fetal demise (IUFD) when there is massive placental

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involvement or umbilical cord damage [5,6]. FTV has also been associated with adverse neonatal outcome, especially neurologic impairment. Previous analyses based on a selected population of children with neurologic disorders such as neonatal encephalopathy, neurologic impairment and cerebral palsy have established a relation between FTV and poor neurological outcome [7–10]. Systemic thrombosis affecting other organs has also been described in association with FTV including pulmonary or kidney thrombosis [11], limb necrosis [12], cardiac infarction [1], intestinal atresia [13] and severe perinatal liver disease [14,15].

To date, no specific ultrasound criterion is reliable enough to diagnose FTV prenatally. It can nevertheless be suspected in cases of IUGR, cord abnormalities, absent or reversed end diastolic blood flow and nonreassuring fetal heart tracing (NRFHT) at delivery [6,16].

The etiology of FTV remains unknown. In theory, it may be due to any of the conditions involved in Virschow's triad: (1) hypercoagulable state, (2) endothelial damage and (3) blood flow stasis or turbulence. Fetal anemia, polycythemia, hypovolemia, maternal diabetes mellitus and thrombophilia are known to be able to induce a hypercoagulable state. Umbilical cord abnormalities (such as excessively long or hypercoiled cord, true knots, abnormal cord insertion, cord entanglement, stricture, prolapse, amniotic bands or amniotic web) can cause endothelial cell injury and stasis or turbulence of the fetal blood flow and seem to be the main causes leading to FTV [17–19].

We undertook this retrospective cohort study to determine the prevalence of obstetric complications, placental abnormalities and adverse fetal, neonatal and early childhood outcome of children whose placentas had FTV compared with an unselected population.

2. Materials and methods

2.1. Case selection

After approval by the Internal Institutional Review Board, the Pathology Department database at Croix-Rousse Hospital (Lyon, France) was searched for placentas received between 2005 and 2009 with a diagnosis of fetal thrombotic vasculopathy. 106 placentas meeting this criterion were identified among a total of 2990 placentas received during this period. We selected only cases for which a clinical follow-up up to 3 years was available (three years being the minimum age at which an evaluation of the neurologic impairment can be made). We requested data from the hospital's clinical and laboratory database to collect clinical information about the mother, the delivery, and the clinical outcome of the child. These data were available for 54 cases, which constituted the final study cohort.

Among the placentas consecutively received during the same period we randomly selected 100 control cases matched for gestational age (1–2 control cases per FTV case). The rate of placental submission for histologic examination in our hospital ranged from 8.2 to 15.2% per year during the study period. According to hospital policy, only placentas associated with maternal, fetal or neonatal conditions, or with morphologic abnormalities should be submitted. Therefore, the histologic findings for the placentas selected as controls for this study are often related to those specific conditions. For each control case, the slides were reviewed to confirm the absence of FTV. Clinical, radiological and laboratory data for these cases were also requested from the hospital database and compiled for the statistical analysis.

2.2. Data collection

For each FTV case and each control case, we retrieved and recorded the following specific information from the electronic medical database: (1) maternal status including type of pregnancy (singleton or twin pregnancy), maternal age, gestational age and method of delivery, emergency or normal delivery procedure and sex of the newborn; (2) obstetric complications including pregnancy-induced hypertension (PIH), preeclampsia (PE), gestational diabetes mellitus (GDM), maternal infection, and premature rupture of membranes; (3) fetal or neonatal conditions including nonreassuring fetal heart tracing (NRFHT), intrauterine growth restriction (IUGR), Apgar score and immediate ex utero adaptation, intrauterine fetal demise (IUFD), termination of pregnancy (TOP); and (4) pediatric follow-up and outcome including neonatal or early childhood demise, morphological abnormalities, which were classified as cerebral (assessed by neonatal encephalography, neonatal transfontanellar ultrasound examination, cerebral MRI, or autopsy in cases of stillbirth or neonatal demise), cardiovascular, or other; psychomotor retardation, sensorineural defect, motor disorders, severe neurodevelopmental delay, mental retardation and behavioral disorders; and any possible thromboembolic events.

Because laboratory assessments of maternal, neonatal and pediatric thrombophilia were available for only a few cases, they were not included in the analysis.

2.3. Pathologic evaluation

The placentas were fixed in 5% formaldehyde for 6–15 days and then examined according to the standardized examination protocols [2] by a senior pathologist. Because the obstetric department did not usually send the entire umbilical cord, we were unable to evaluate length. Standard sampling included at least one section of the umbilical cord and membrane roll and a minimum of 2 sections of the placental parenchyma. All macroscopic lesions were sampled. Hematoxylin eosin saffron (HES) stained slides were prepared for histological examination. All placental slides of the selected cases were reviewed by 2 pathologists blinded to clinical information (except for gestational age).

The diagnosis of fetal thrombotic vasculopathy was confirmed if any of the following findings were made [2–4,9,20]:

- Avascular villi (AV), defined as 1 or more foci involving at least 15 contiguous terminal villi and showing a total loss of villous capillaries and bland hyaline fibrosis (uniformly avascular villi – UAV), or karyorrhexis of fetal cells with preservation of surrounding trophoblast (villous stromal–vascular karyorrhexis – VSVK) or villitis of unknown etiology (VUE) extending to stem villi with vascular occlusion
- Thrombosis in the fetal circulation, defined as mural or occlusive fibrin clots adherent to the endothelium on at least one side of a large vessel (umbilical cord, chorionic or stem vessel),with or without calcification
- Endothelial cushion (EC), defined as laminated fibrin deposited in the intima and fibroblast proliferation bulging out into the lumen of a large vessel, or calcification in the wall of the vessel.
- Hemorrhagic endovasculitis (HEV), defined as loss of integrity of the vascular wall of a large vessel, with fragmentation and extravasation of red blood cells in the stroma, and septation in case of partial organization.

Isolated AV or HEV were excluded in cases with IUFD since they are standard findings in this condition [2,21]. Diagnosis of FTV in a placenta with IUFD required a histological finding of thrombosis or EC.

Apart from FTV lesions, we recorded the presence of the following other placental lesions: chronic villitis, chorioamnionitis, villous hypoxic changes (Tenney Parker changes), infarction, decidual vasculopathy, retroplacental hematoma, chorangiosis, chorangioma, intervillous thrombi, massive perivillous fibrin deposition, and intervillositis.

These findings were tabulated with all the clinical data collected.

2.4. Statistical analysis

Continuous variables were described with their means, standard deviations, medians and quartiles. Categorical variables were described with frequencies and percentages of each category.

Wald's chi-square was used to assess the statistical significance of differences between the cases and control cases study groups. We used conditional logistic regression, taking into account the matching between cases and control observations, to estimate odds ratios (OR) and their 95% confidence intervals (CI) [22]. In some cases with only a few events (e.g. thromboembolic events), exact conditional logistic regression was performed. A two-sided P value of <0.05 was considered significant. SAS software (Windows V9.2) was used for all statistical analyses.

3. Results

Microscopic FTV lesions were confirmed in all the retrieved cases with a diagnosis of fetal thrombotic vasculopathy for which the additional clinical and outcome data were available (Fig. 1). The FTV group included 46 singleton and 4 dichorionic–diamniotic twin pregnancies. The control group included 86 singleton and 7 dichorionic–diamniotic twin pregnancies. The FTV group consisted of 35 male and 19 female fetuses (vs 51 and 49 respectively in the control group). The mean maternal age was similar in the FTV and control groups (mean 30.72 years (range 18–39 years) vs 30.02 (range 19–42)). The mean gestational age at delivery was similar in both groups: 29.95 weeks (range 22.86–40.57) for the FTV group and 29.94 weeks (range 22.28–40.71) for controls.

Clinical and pathologic findings are detailed in Table 1. Obstetric complications were substantially more frequent in the FTV population, including a 3.6-fold increase for PIH (95% CI: 1.6–8.4) and a