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Distribution and potential significance of intravillous and intrafibrinous particulate microcalcification

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ABSTRACT

Radiologic studies indicate that placental calcifications seen at 28–32 weeks' gestation are associated with adverse fetal outcome. One type of placental calcification is typically located at the basement membrane of chorionic villi. It has a fine particulate appearance and can only be seen microscopically. We have designated these calcifications as Intravillous and Intrafibrinous Particulate MicroCalcification (IPMC). In this study we examined the distribution and potential significance of IPMC. Placentas from 14 groups of fetal and maternal outcomes are examined histologically for IPMC. These groups were preterm birth, post term birth, intrauterine fetal demise, fetuses with non-reassuring heart rates, intrauterine growth restriction, fetal anomalies, mothers with gestational hypertension, gestational diabetes, placental abruption, pre-eclampsia and placentas of normal spontaneous vaginal births and placentas with chorioamnionitis, chronic villitis and infarcts. We observed fine dust-like particulates deposited in continuous and discrete patches. The particulates were predominantly located in the basement membranes of fibrotic chorionic villi and in perivillous fibrin. Compared to placentas without adverse outcomes, a higher incidence of IPMC was seen in intrauterine fetal demise cases and in cases with infarcts which suggests that hypoxia played a role in the etiology of IPMC.

1. Introduction

Placental calcifications observed on ultrasound imaging was once used clinically to assess the level of maturation of a placenta as it correlated with fetal lung maturation [1]. The placenta grading system developed by Grannum et al. [1], is three-tiered with a grade III mature placenta characterized by echogenic indentations throughout the placenta. However, this system is not reliable at predicting advanced maturity since the reported prevalence rate of grade III placenta at term (37–40 weeks) is variable. In some studies this prevalence rate ranges from 17.7% to 39.4% [2–4].

There is a type of placental calcification that is typically located at the basement membrane of chorionic villi and can be only seen microscopically. Less frequently, they are also seen in villous stroma and perivillous fibrin. We have designated these calcifications as Intravillous and Intrafibrinous Particulate MicroCalcification (IPMC). These microcalcifications are fine, particulate and basophilic in appearance on hemotoxylin and eosin stain, and stain for calcium on Von Kossa stain. With heavy deposition, IPMC appear as linear deposits along the basement membrane.

The etiology and significance of IPMC is not well understood. In this study we examined the distribution and potential significance of IPMC.

2. Material and methods

Placentas with the following clinical and histopathologic diagnoses were retrieved from the pathology departmental database at NYU Langone Medical Center between January 2014 and June 2015: preterm birth (21 cases), post term birth (21 cases), non-reassuring fetal heart rate (19 cases), intrauterine fetal demise (19 cases), intrauterine growth restriction (20 cases), chorioamnionitis (19 cases), fetal anomalies (19 cases), placental infarcts (19 cases) and chronic villitis (20 cases). In addition, placental cases from mothers with gestational diabetes (20 cases), placental abruption (20 cases), pre-eclampsia (20 cases), and hypertension (20 cases) were included. During the same time frame, placentas from 18 cases of normal spontaneous vaginal delivery were selected to serve as control cases.

Placentas were examined for IPMC by one of the authors (JZ),

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who is not blinded to the case histories. At our institution, the standard histologic examination of a placental specimen is two full thickness sections from either side of the cord insertion, approximately half way between the cord insertion and the edge of the placenta. Additional sections were taken from areas that grossly appeared concerning.

Location and percentage of villi affected by IPMC were recorded. Percentage of villi involved by IPMC was compared between different groups of placentas and quantified as less than 1%, 1–5%, 5–10% and greater than 10%. The location of the IPMC was recorded as within the fibrinoid areas around the villi or within the basement membrane and/or stroma of villi. Statistical calculations were done using Fisher's exact test. All p values are two tailed.

3. Results

IPMC were seen in all placental groups to varying degrees and in multiple foci (Table 1). Of the total number of cases included in the study, IPMC involved less than 1% of villi in 124 of 275 cases (45%), 1–5% of villi in 54 of 275 cases (20%), 5–10% of villi in 21 of 275 cases (8%) and greater than 10% of villi in 13 of 275 cases (5%).

IPMC in >5% of villi were not seen in any placentas from the 18 normal vaginal deliveries, but were present in 12 of the 18 cases with fetal demise ($p = 0.0001$), 11 of the 19 infarcts ($p = 0.0001$), and 5 of the 21 cases with post term birth ($p = 0.05$). In cases of acute chorioamnionitis, diabetes, chronic villitis, abruption, and pre-eclampsia, the presence of IPMC in >5% of placental villi were not statistically significant (Table 1). Increased IPMC were not seen in placentas from patients with hypertension, and fetuses with non-reassuring fetal heart tracings.

In the fetal demise cases, IPMC involved greater than 10% of villi in 7 of 19 cases (37%), whereas in the live birth cases, IPMC involved greater than 10% of villi in only 6 of 259 cases (2%, $p < 0.0001$). In addition, IPMC was more frequent in cases of fetal death where the fetus remained in utero for a longer period of time after demise. Clinical data was available for 8 of the 19 intrauterine fetal demise cases (Table 2). Of these 8 cases, 5 cases remained in utero for less than 1 day while in 3 cases, the fetus was retained in utero for one or more days after demise. IPMC involving greater than 10% of villi were seen in 2 of the 3 cases where the fetus remained in utero for one or more days after demise, compared to none of the 5 cases where intrauterine retention was less than 1 day. The difference however did not reach statistical significance due to the small number of cases in each group ($p = 0.10$). The IPMC were mostly located within the basement membranes of villi with perivillous fibrin, and within the perivillous fibrin (Fig. 1). However, IPMC were also present in otherwise seemingly normal villi, without any perivillous fibrin (Figs. 2 and 3).

Placentas with macroscopic infarcts show markedly increased IPMC within areas of infarction (Fig. 4). Within these areas, the deposits of IPMC are highlighted by Von Kossa stain (Fig. 5). IPMC involved greater than 90% of the infarcted areas in 5 of 19 cases (26%), 50–90% of the infarcted areas in 8 of 19 cases (42%) and 10–50% of the infarcted areas in 6 of 19 cases (32%). The distribution of IPMC in infarcts was different from other cases in that IMPC were more diffusely present in villous stroma away from trophoblastic basement membrane. IMPC were not increased in non-infarcted areas of placentas with infarcts.

4. Discussion

Placental calcification on ultrasound is rarely seen before 37 weeks. In fact, their presence before 37 weeks may indicate pathologic accelerated maturation of the placenta. These calcifications are called pre-term placental calcifications and they are associated with a number of fetal and maternal complications. The fetal complications include intrauterine growth restriction, low birth weight, fetal distress and low Apgar scores [3,5–9]. Preterm ultrasound detected placental calcifications are associated with a maternal history of smoking, and maternal complications, including pregnancy induced hypertension, pre-eclampsia, placental abruption and postpartum hemorrhage [6,8,10]. However, other studies report that preterm placental calcifications are not associated with these findings [4,11]. Placental calcifications are also associated with viral infections from rubella, cytomegalovirus, herpes simplex and varicella zoster [12,13]. In these cases, congenital infections can cause a number of fetal malformations detectable by ultrasound, from microcephaly, micrognathia to hepatosplenomegaly and intracranial calcification. These congenital infections can also cause placental changes, including calcification which may or may not be seen on ultrasound.

IPMC are a distinct form of placental calcifications that are predominantly located at the basement membranes of chorionic villous epithelium. The purpose of this retrospective cohort study is to clarify the association between IPMC and adverse maternal and fetal outcome using histomorphology.

IPMC were seen in all placental groups with different clinicopathologic diagnoses to varying degrees. In general they were an infrequent finding in placentas across all placental groups (Table 1). Across categories, the majority of placentas had less than 1% of villi with IPMC. We found increased IPMC in cases of intrauterine fetal demise and cases with placental infarcts, compared to other placental categories and normal vaginal delivery controls.

Calcifications that we have designated IPMC have been previously described in the literature as material deposits in the basement membrane of the chorionic villus underneath trophoblastic cells and are attributed to histologic changes that follow intrauterine fetal demise which accompany maceration [14,15].

The etiology for IPMC is still unknown, however there are a number of theories including dysfunctional placental calcium pumps, oxidative stress and nanobacteria [10,16–25]. Early authors believed placental calcification were seen upon fetal death as a result of disrupted maternal-fetal circulation leading to impaired calcium transport across syncytiotrophoblast basement membrane from the mother to the fetus. However, this does not explain the occurrence of IPMC we observed in perivillous fibrin. In addition, if impaired calcium transport across syncytiotrophoblast is the underlying mechanism for placental calcification, then this raises the question for the triggering factor(s) causing this series of events.

Similar to previous observations, we found higher concentrations of IPMC in intrauterine fetal demise cases compared to other categories. In fact, IPMC was more frequent in cases of fetal death that stayed in utero for longer period of time. Although Avery et al. [14] concluded that placental calcifications were commonly seen in stillbirths, they have since been reported in live pregnancies. In 2003, Kasznica et al. [26] reported intravillous calcification in a voluntarily terminated second trimester pregnancy with cardiac anomalies. In our study, the association of IPMC with infarcts, fetal demise and perivillous fibrin raises the possibility that IPMC may be a response to a local hypoxic environment. However, as IPMC were also seen in otherwise histologically normal villi, there remains the possibility that IPMC may be a primary event, or markers of a primary event that leads to perivillous fibrin and hypoxia. These findings, taken together, raise the possibility that IPMC may result from absent or reduced fetal circulation that would be seen in IUFD and also in infarcts. This reduced fetal circulation could then lead to reduced calcium removal from local microenvironment, leading to it's deposition as IPMC.

Radiologic studies show that placental calcification in high-risk mothers is a predictor for a number of adverse maternal and fetal