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The role of preterm placental calcification on assessing risks of stillbirth☆

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ABSTRACT

Introduction: Stillbirth is an important issue in antenatal care and much remains unknown. This cohort study aims to explore the previously un-identified risk factor of third-trimester stillbirth to determine if Grade III preterm placental calcification (PPC) is associated with stillbirth.
Methods: At a tertiary teaching hospital, obstetric ultrasonography was performed at 28 weeks' gestation to establish a diagnosis of PPC. Pregnancies with multifetal gestations, major fetal congenital anomalies, termination, cord accidents, apparent intrauterine infection, and antepartum complications were excluded.
Results: 15,122 eligible pregnancies were categorized as stillbirth (n = 99) and livebirth (n = 15,023) groups. Between these two groups, there were no significant differences in maternal age, BMI, and parity, but significant differences in smoking and in PPC (35.4% vs 6.3%, $p < 0.001$) were observed. The peak occurrence of stillbirths was at 30 and 37 weeks' gestation, with a bimodal distribution of 11 and 17 stillbirths, respectively. For pregnancies with or without PPC, the incidences of stillbirths per-1000-births were 35.9 and 4.5, respectively. Using Kaplan–Meier survival analysis, at 40 weeks' gestation the cumulative stillbirth risk for pregnancies with PPC was higher compared to those without PPC. Logistic regression revealed that after adjusting for the effects of smoking and demographic factors, the risk of stillbirth (adjusted OR:7.62; 95% CI:5.00–11.62) was much higher when PPC was present.
Discussion: Grade III PPC is associated with a higher incidence of stillbirth, and identified an independent risk factor. Being a pathologic implication, it may precede this negative outcome and can serve as a warning sign or marker when noted on ultrasonography.

1. Introduction

Stillbirth or intra-uterine fetal death (IUFD), defined by the World Health Organization as fetal death after 28 weeks' gestation, has huge repercussions for parents, their families and clinicians. It is responsible for an estimated 2.65 million deaths worldwide each year [1], with an overall prevalence of 0.5–1% of pregnancies [2–5]. Stillbirth is one of the least studied obstetric complications [6], largely due to the relatively low percentage of postmortem examinations [2]. Even after fetopsy and placental examination, approximately 50% of stillbirths remain unexplained [7]. Common etiologies of stillbirths include placental insufficiency, intrauterine infection, and cord accidents [3,5,6,8–12], in which non-acute cord compression is implicated in over half of unexplained third trimester stillbirths [7,13]. Other identified maternal or fetal vascular supply abnormalities are hematoma, thrombus, and infarcts [10,12,14]. According to an emphasis on either pathological information or clinical details, different systems (e.g., Tulip classification [15]) have been developed for classifying perinatal mortality, thus resulting in different interpretations regarding what has happened. However, many of the etiologies or findings of stillbirths are disclosed postmortem. If clinicians are able to find some signals before fetal demise, maybe they can report the risk, provide

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information, enhanced monitoring or earlier intervention in advance to reduce the occurrence of stillbirth.

Placental calcification, often noted on ultrasound examination during pregnancy, is characterized by widespread deposition of calcium on the placenta, resulting in echogenic foci. When the process has advanced to the deposition of calcium on the basal plate and septa, calcification may appear to be linear or even circular [16–18]. Grannum classification via either manual [19] or computerized assessment [20], has been used for ultrasound placental grading. Grade III placental calcification, characterized by significant formation of indentations or ring-like structures within the placenta [16] (Fig. 1), is often found in term pregnancy and regarded as a physiological aging process without clinical significance [16–18] as demonstrated by a study which found no correlation between placental grading and placental function in the third trimester [21]. However, the presence of calcification before 36 weeks' gestation (preterm placental calcification) may represent an unusual change. McKenna et al. [22] reported that grade III placental calcification at 36 weeks' gestation was associated with pregnancy induced hypertension and fetal growth restriction. Abnormal placental appearance (e.g. placental calcification or lake) at second trimester ultrasound scan was found to correlate with placental infarction and uteroplacental dysfunction [23]. Proud and Grant confirmed the association between Grannum grade III placenta and poor condition at birth or perinatal death [24]. Furthermore, we have found that preterm placental calcification (PPC) is a major risk factor of adverse maternal and neonatal outcomes including preterm delivery, low birth weight, low Apgar scores, and neonatal death in both low-risk and high-risk pregnancy populations [25,26]. In case of placental dysfunction or failure, the survival of the infant may depend upon the magnitude of the placental insult, which implies that placental assessment is a key to save babies' lives [27]. If stillbirth represents the earlier and most serious consequence after a fetus sustains a critical hit or long-term uteroplacental compromise, we believe the etiology that underlies the poor neonatal outcome may contribute to third trimester stillbirth via similar mechanisms. Thus, the purpose of this study is to determine if the presence of Grade III PPC is associated with stillbirth.

Fig. 1. Grade III placental calcification according to the Grannum classification. Diffuse echogenic lines (indentations) extending from the chorionic plate to the basal layer are noted.

2. Methods

2.1. Study design and sample

This prospective, cohort study was conducted in a tertiary teaching hospital with an average of 200 or more deliveries per month. The hospital provides a routine obstetric clinic (available to all women) for general low-risk pregnancies, and a special obstetric clinic (requiring referral) for high-risk pregnancies. All pregnant women can receive prenatal care in the routine obstetric clinic without referral. All women with antenatal complications noted in the routine clinic or at other hospitals are transferred to our special obstetric clinic for evaluation and management of high-risk pregnancy. The study was approved by the local Institutional Review Board of the hospital.

Pregnant women were screened by obstetric ultrasonography at 28 weeks' gestation to establish the diagnosis of PPC. Grade III placental calcification is defined by the presence of echogenic indentations extending from the chorionic plate to the basal layer dividing the placenta into discrete components, resembling cotyledons. All ultrasound examinations were performed using a Voluson 730 (GE Medical Systems, Zipf, Austria) equipped with a 2.8–10-MHz transabdominal transducer, by 1 qualified obstetrician to avoid inter-observer bias. All images were further reviewed by another experienced obstetrician to ensure the accuracy of the diagnosis. Between the observer and the reviewer, there is agreement on most images (957/974 images for the presence of Grade III PPC and 14,120/14,148 images for no presence of Grade III PPC). The observer–reviewer agreement was excellent (Kappa = 0.975). There were only few discrepancies of classification (17 observer-identified Grade III PPC among 974 images and 28 observer-identified no Grade III PPC among 14148 images), which were further corrected after a final joint review of the two physicians.

All pregnancies of women in the obstetric clinics were considered for the study. Initial screening was performed to exclude pregnancies of women who did not deliver at our hospital, or had missing data in the medical record. Because smoking can compromise uteroplacental blood flow [16,28], and is a risk factor for stillbirth [6,29–31], women who smoked or did not smoke during their pregnancies were included and evaluated in the study. On the other hand, pregnancies with multifetal gestations, major fetal congenital anomalies, termination before 24 weeks' gestation, cord accidents, apparent intrauterine infection, and antepartum complications (hypertension, diabetes mellitus, placenta previa, marked anemia), all of which can affect the fetus and be possible confounders [3,5,6,8,30,31], were excluded from this study. Except for the women who met the abovementioned exclusion criteria, all pregnancies were enrolled by means of an ordinary survey rather than obstetrician's preference (highly selected samples), so as to decrease selection bias.

Basic information including age, body mass index (BMI), and parity, all of which have been recognized as potential risk factors of stillbirth [5,6,29–31], as well as general medical history, were obtained at the first antenatal visit. The determination of gestational age was principally based on the last menstrual period, and validation of true gestational age was confirmed by ultrasound measurement of fetal development in early pregnancy. If there was a significant discrepancy (>1 week) between them, another ultrasound scan was performed to confirm the gestational age. Ascertainment of smoking during pregnancy, identification of multifetal pregnancy, major congenital fetal anomalies, or placenta previa by using ultrasonography, the diagnoses of marked anemia, chronic or pregnancy-induced hypertension, and gestational or overt diabetes were made on subsequent visits between 12 and 28 weeks' gestation. Maternal and newborn outcomes were recorded at