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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.

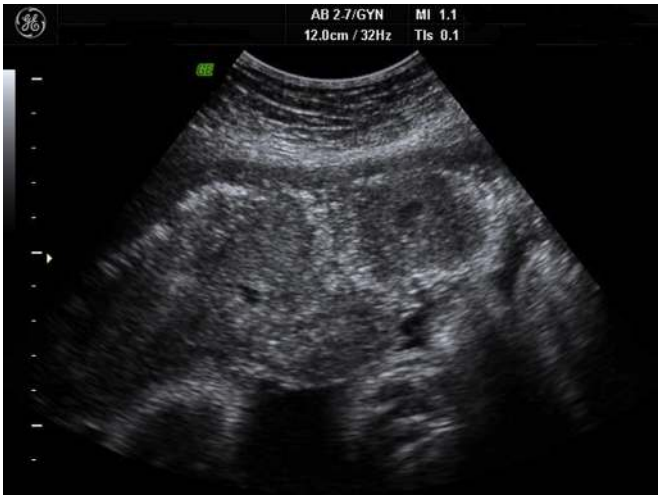

Fig. 1. Grade III placental calcification according to the Grannum classification. Diffuse echogenic lines (indentations) extending from the chorionic plate to the basal layer are noted.

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

delivery. The occurrence of cord accidents and apparent intrauterine infection were also checked after delivery.

2.2. Data analysis

Data were collected and analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). The statistics used included descriptive statistics, chi-square (χ^2) test, and student t test as appropriate to compare the characteristics and outcomes of pregnant women. Kaplan–Meier survival analysis was used to estimate the cumulative risk of stillbirth after 28 weeks' gestation. Logistic regression analysis was performed to compare differences of stillbirth rates among women with or without PPC, and who smoked or did not smoke, adjusted by maternal age, BMI, and parity. Odds ratios (OR) and 95% confidence intervals (CI) were calculated after adjusting for the effects of abovementioned factors.

3. Results

There were 19,338 pregnancies of women who received antenatal examinations at the obstetric clinics. After initial screening with excluding women who did not deliver at our hospital or had missing data (n = 1547), 17,791 pregnancies were eligible for further analysis. A total of 15,122 pregnancies of women who met the inclusion criteria were enrolled after further excluding those who had multifetal gestations, major fetal congenital anomalies, terminated pregnancy before 24 weeks' gestation, cord accidents, apparent intrauterine infection, or antepartum complications such as hypertension, diabetes mellitus, placenta previa and marked anemia (n = 2669). Of the 15,122 pregnancies 99 had stillbirths and the other 15,023 had livebirths.

The characteristics of the women in the stillbirth and livebirth groups are shown in Table 1. In the 2 groups, the average maternal age was about 27 years, and the average BMI was around 21 kg/m^2. During pregnancies, there were no significant differences in maternal age, BMI, and parity between the 2 groups, but there were significant differences in smoking and PPC ($p < 0.001$). In the stillbirth and livebirth groups, the majority of women were nulliparous (52.5% and 53.6%, respectively), did not smoke (63.6% and 85.6%), and were not found to have PPC on ultrasonography (64.6% and 93.7%). However, there was a greater frequency of PPC in the stillbirth group than the livebirth group (35.4% vs. 6.3%). The average gestational lengths in the stillbirth and livebirth group were 34.74 and 38.27 weeks, and the birth weights 2240.05 and 3151.44 g, respectively. As expected, shorter gestations and lower birth weights were noted in the stillbirth group.

Fig. 2 illustrates the distribution of all stillbirths during the third trimester. The peak occurrences of stillbirths were at 30 and 37 weeks' gestation, with 11 and 17 stillbirths, respectively. Fig. 3 illustrates the cumulative risk of stillbirths for pregnancies with (solid line) and without (dotted line) the presence of PPC. Kaplan–Meier survival analysis indicated that at 40 weeks' gestation the cumulative risk of stillbirth for pregnancies with PPC was higher as compared to those without PPC.

The results of the risk assessment for stillbirths are shown in Table 2. For pregnancies of women who smoked and did not smoke, the incidence of stillbirth per 1000 births was 16.3 and 4.9, respectively. For pregnancies with or without PPC, the incidence of stillbirth per 1000 births was 35.9 and 4.5, respectively. Logistic regression analysis was performed to compare the difference of stillbirth rate among all enrolled pregnancies adjusted by maternal age, BMI, and parity. The risk of stillbirth was greater in pregnancies of women who smoked than those that did not (adjusted OR 3.16; 95% CI: 2.08–4.80, $p < 0.001$). Even after adjustment for the effects of smoking and abovementioned demographic factors, the risk of stillbirth was much greater in pregnancies of women who had PPC than those that did not (adjusted OR 7.62; 95% CI: 5.00–11.62, $p < 0.001$).

4. Discussion

The results of this study revealed that Grade III PPC (noted at 28 weeks' gestation) is associated with a higher incidence of stillbirth. Grade III PPC is a significant and independent risk factor (adjusted OR 7.62; 95% CI: 5.00–11.62) for stillbirth, in addition to smoking. Being a pathologic implication, the presence of Grade III PPC may precede this negative outcome and can serve as a warning sign or marker when noted on ultrasonography, and requires closer surveillance for fetal well-being.

Although other grading of PPC is not the major concern of this study, its effect on perinatal outcome is also checked. Our data revealed that in the stillbirth group the percentages of finding Grade I, II PPC and No PPC at 28 weeks' gestation were 4.7% (3/64), 6.3% (4/64) and 89.1% (57/64), respectively among all eligible women. In the livebirth group the percentages of finding Grade I, II PPC and No PPC at 28 weeks' gestation were 5.0% (703/14,084), 6.0% (844/14,084) and 89.0% (12,537/14,084), respectively among all

Table 1
The characteristics of the women during their pregnancies.

Pregnancies	Stillbirth (n = 99)		Livebirth (n = 15,023)		*p* value
Age (year)	26.91	±2.31	26.81	±2.07	0.637
Body mass index (kg/m^2)	21.70	±1.12	21.58	±1.16	0.285
Parity					0.963
1	52	(52.5)	8053	(53.6)	
2	32	(32.3)	4826	(32.1)	
3 or more	15	(15.2)	2144	(14.3)	
Smoking					<0.001*
Yes	36	(36.4)	2167	(14.4)	
No	63	(63.6)	12,856	(85.6)	
Grade III preterm placental calcification					<0.001*
Yes	35	(35.4)	939	(6.3)	
No	64	(64.6)	14084	(93.7)	
Delivery data					
Gestational length (week)	34.74	±3.66	38.27	±1.93	<0.001*
Birth weight (gm)	2240.05	±907.15	3151.44	±480.73	<0.001*

*$p < 0.001$, by chi-square test or student t test, as appropriate.
Data are expressed as number (%) or mean ± standard deviation, as appropriate.

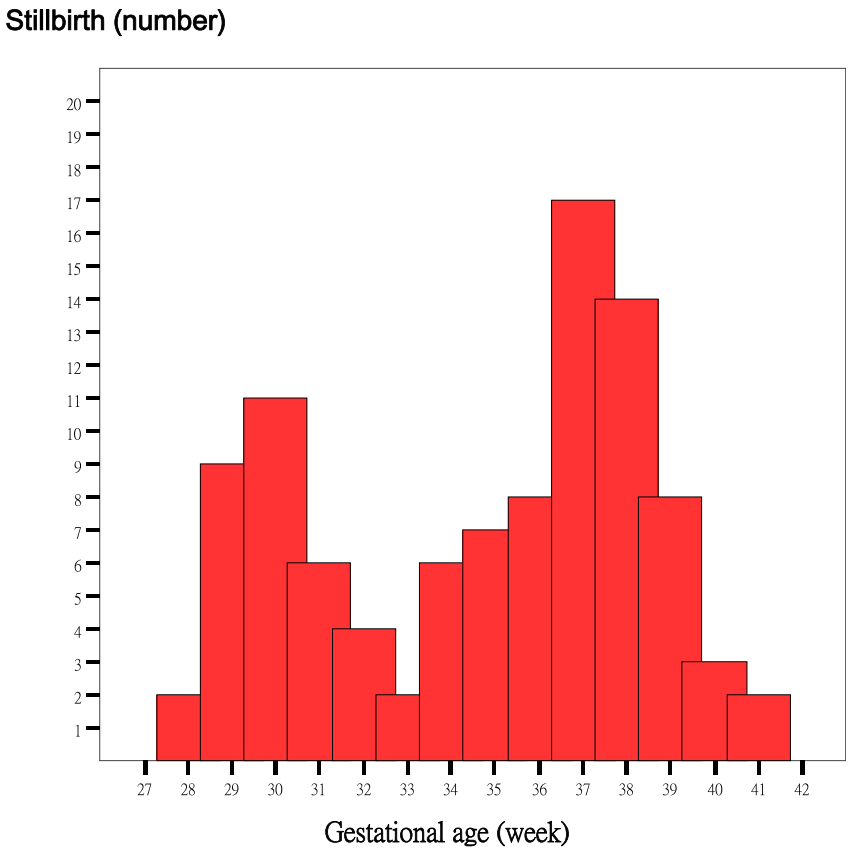

Fig. 2. The distribution of all stillbirths during the third trimester (28–41 weeks' gestation).

eligible women. Although Grade I and II PPC were not the focus of the study, the incidences of stillbirth were not elevated in women with Grade I and II PPC when compared with those without any PPC ($p > 0.05$). In brief, other types (Grade I and II) of PPC are not associated with increased risk of stillbirth.

Despite extensive research, currently the clinical tools for screening and diagnosis of placental dysfunction lack sensitivity and specificity to predict SGA or to prevent stillbirths in a cost-effective way [27]. For example, umbilical artery Doppler has a sensitivity of 19% and specificity of 91% for the prediction of SGA in a low-risk population [32], which rises to a sensitivity of 55% and a specificity of 85% in high-risk cases [33]. In our study, among the 15,122 pregnancies 99 had stillbirths and the other 15,023 had livebirths. The incidence of stillbirth was 0.7%. A total of 35 Grade III PPC (35.4%) was found among 99 stillbirths. Thus, we would need to scan 432.1 women to prevent one stillbirth (35/15,122). The results of the study also means that over one third (35.4%) of all stillbirths can be detected and saved after performing ultrasonography. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of Grade III PPC for stillbirth are separately calculated as 35.4% (35/99), 93.7% (14084/15,023), 0.036 (35/974) and 0.996 (14084/14,148). Considering the incidence (0.5–1%) and low detectability of stillbirth, cost, benefit and the fact that currently there's no good tool for assessment, an ultrasonic evaluation with the identification of Grade III PPC provides useful information for the assessment of stillbirth risk among low-risk population.

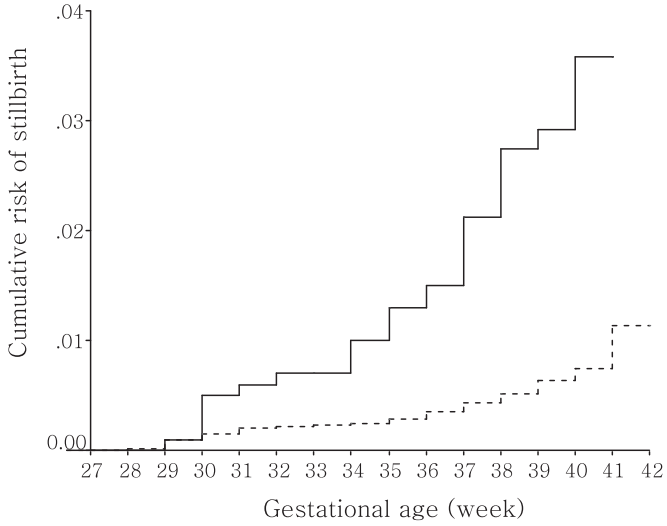

Fig. 3. The cumulative risk of stillbirths for pregnancies with Grade III preterm placental calcification (PPC) (solid line) and without (dotted line) by Kaplan–Meier survival analysis.

A possible explanation for PPC to impair uteroplacental function and result in subsequent fetal death is gradual occlusion of vessels after deposition of calcium and fibrin [34]. This explanation is supported by the pathological finding that placentas in fetal Bartter syndrome exhibit extensive basement membrane mineralization [35], focal calcification, and acute atherosclerosis in the placental vessels [36]. Placental depositions on the basal plates have also been found to cause maternal floor infarction [23], and are associated with intrauterine growth restriction and mid-trimester loss [10]. Other studies confirmed the findings of calcification and thrombi, both of which occluded chorionic and umbilical vessels

Table 2
Risk assessment of stillbirth.

	Stillbirths	Total births	Stillbirth rate (per 1000 births)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)	*p* value
Smoking						
Yes	36	2203	16.3	3.39 (2.25–5.12)	3.16 (2.08–4.80)	<0.001*
No	63	12,919	4.9	—	—	Reference
Grade III Preterm placental calcification						
Yes	35	974	35.9	8.20 (5.20–12.45)	7.62 (5.00–11.62)	<0.001*
No	64	14148	4.5	—	—	Reference

CI, confidence interval.
*$p < 0.001$, calculated by logistic regression analysis.
Adjusted odds ratio was measured with adjustment of other variables including age, body mass index, and parity.
— indicates no data.

[9,37] and contributed to severe intrauterine fetal growth restriction, and were associated with the finding of absent end diastolic velocity (AEDV) in the umbilical artery [37]. However, the true mechanism seems complicated and remains for future research to address the primary etiology underlying the clinical manifestations and outcomes.

The results of this study suggest that PPC in pregnant women is not physiologic, but pathologic, which implies that early calcification could have a different mechanism from that of placental calcification at term, when calcium deposition proceeds in such a supersaturated environment and eventually results in marked calcification of the placental basement membrane [38]. In contrast, PPC originating from early and excessive calcium build-up in the placenta maybe a dystrophic change, and may contribute to further tissue damage. As mentioned in the studies Agababov et al. [39] and Pasquinelli et al. [40], nanobacteria could play a critical role in the initiation of early pathologic placental calcification. Unlike physiological calcification, the accelerated and excessive deposition of calcification initiated by nanobacteria might be destructive to tissues, precipitating the negative outcome. Detailed discussion of the calcification cascade is beyond the scope of our study, but we believe that further effort should be given to explore the relationships between the calcium pump, nanobacteria, and pathologic placental calcification.

To our best knowledge this is the first report using 2-dimensional ultrasonography for assessing the risk of stillbirth. Although pathologic examination can provide a more detailed understanding about what has caused a stillbirth [3,6,9,41], it cannot be done before a dead fetus is delivered, and cannot be used to prevent its occurrence. In addition, in many countries cultural traditions will not allow postmortem examination of a stillbirth. Furthermore, many parents do not want their fetuses to undergo autopsies and associated pathologic examinations of the placentas and cords. Therefore, exploration or confirmation of the possible etiologies cannot be obtained by means of pathologic examinations.

Two studies have examined the role of uterine artery Doppler (UAD) ultrasound on estimating the risk of stillbirth [42,43]. For at-risk fetuses diagnosed by UAD, an intervention with induction of labor was proposed to prevent stillbirth [43]. Although UAD findings can serve as a good marker for stillbirth, UAD is usually performed on high-risk populations [42,43], and hence the application is somewhat limited. In contrast, our study focused on a general population, and may have a wide application for the general assessment of the risk of stillbirth.

There are limitations to this study that should be considered. The population that we studied was women receiving care at a tertiary hospital, and thus generalization of the conclusions to other women visiting smaller hospitals or local clinics should be made with caution. Characteristics such as race, socio-economic and educational status were not considered, and could affect the results. The study was conducted in a smaller Eastern country, so the effect of race on stillbirth was not examined. As a longitudinal study, the last limitation concerns some uncontrolled factors that varied with time and change of medical policies.

In conclusion, Grade III PPC is not an aging progress but a reflection of underlying placental dysfunction when noted at 28 weeks' gestation. Close attention should be paid to women with Grade III PPC since this ominous sign is associated with an increased risk of stillbirth. Although this study has provided some helpful messages, many unknown aspects regarding stillbirth warrant further investigation.

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None declared.

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