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Sonographic assessment of Placental calcification pattern in pregnancy induced hypertensives

Efanga SA[1], Akintomide AO[1], Obiora CI[2], Efanga I[3].
[1]*Radiology Department, University of Calabar, Calabar, Cross River State, Nigeria.*
[2]*Radiology Department, University of Calabar Teaching Hospital, Calabar, Cross-River State, Nigeria*
[3]*Radiography Department, University of Calabar, Calabar, Cross River State, Nigeria.*

Abstract:
Background: *Placental calcification is regarded as a sign that the placenta is ageing with a resultant decline in its performance that might place the pregnancy at a risk of poor fetal outcome. Placental calcification can be accelerated to appear early in pregnancy induced hypertension (PIH) amongst others. We have selected this study to evaluate the pattern of placental calcification in PIH.*
Material and Methods: *This was a prospective cross-sectional case-control study conducted over a 16-month period in the University of Calabar Teaching Hospital that involved 200 PIH women and 200 normotensive pregnant women. An obstetric ultrasound scan was done on all the subjects to examine the placenta. SPSS version 20 was used to analyze the data.*
Results: *Placental calcification had a significant positive correlation with Estimated gestational age (P 0.000) Estimated fetal weight (P 0.000) but a significant negative correlation with Head circumference to Abdominal circumference ratio (HC/AC) (P 0.000) in both groups. Placental calcification had no significant correlation with the systolic (P 0.233) and diastolic (P 0.294) blood pressures in the PIH group and none was seen with proteinuria (P 0.601).*
Conclusion: *The incidence of accelerated placental calcification in pregnancy induced hypertension is double that of the normotensive, though not statistically significant. However, placental calcification is significantly related to the emergence of asymmetrical IUGR and the early appearance of Grannum grade 2 is implicated as a likely trigger for IUGR.*
Key words*: Placental calcification, Intra-uterine growth restriction, Grannum grade, Pregnancy.*

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I. Introduction

Placental calcification is the deposition of calcium phosphate in placental tissue and this occurs with or without a placental disease. [1] Placental calcification is considered to be an expression of placental aging. The possible mechanisms responsible for placental calcification include; physiological pathway (similar to bone matrix mineralization), dystrophic pathway (related to ischemia) or metastatic processes (mineralization in a supersaturated environment). [2]

Placental calcification is diagnosed by using ultrasonography, which is a non-invasive examination, to detect echogenic foci within the substance of the placenta. A thorough examination of the placenta in utero should always be a priority during an obstetric scan since it provides illumination on the health status of the fetus and the mother. Early placental calcification is also a marker of the presence of a viral infection. [1, 3]

Grannum classification system is utilized to grade placental calcification. They are classified into grade 0, grade 1, grade 2 and grade 3. In Grannum grade 0 the placenta has a homogenous echotexture with minimal calcium phosphate deposition. Grannum grade 3 has an incidence of 39.4% at term. [1, 2]

An accelerated appearance of placental calcification has been shown to be connected to PIH, IUGR, smoking, low parity, young maternal age and fetal distress. These events have been implicated in the resulting perinatal morbidity and mortality that occur following placental calcification detection. A delay in the appearance of placental calcification is connected to gestational diabetes and Rhesus (RH) incompatibility. [2, 4, 5] Early appearance of placental calcification may be used to predict high risk pregnancies. [1] In fact, the detection of Grannum grade 3 placental calcification before the 36th week of gestation identifies the pregnancy that is at a high risk. [5, 6, 7, 8]

There is a paucity of knowledge on the mechanism in which the physiological efficiency of the placenta is affected by its calcification. Therefore, a diagnostic approach based on the Grannum classification appears not to be practicable since the managing physician may not be completely certain of any placental impairment. [1]

There is a dearth in clinical research in humans on placental calcification interactions with acute clinical outcomes and moreover, the results from these few studies are discordant. Population characteristics, sample size and differences in gestational ages of the subjects in the various researches may be the reason. [1] The mediating effects of potential confounders such as cigarette smoking, gestational diabetes and PIH have not been profoundly investigated in several studies, [2] and an indigenous study is essential as well.

The aim of this study is to evaluate the pattern of placental calcification in PIH and to assess its effect on fetal growth.

II. Material and Methods

This research was a prospective cross-sectional case-control study conducted at the Radiology Department of the University of Calabar Teaching Hospital, Calabar, Cross River State, Nigeria. The study duration was from August 2017 to November 2018. The study population was obtained from the pregnant women who were attending the Antenatal clinic of the Obstetrics and Gynecology Department of the University of Calabar Teaching Hospital, Calabar, Cross River State, Nigeria.

The subjects who participated in this research were 400 pregnant women. They were placed in two groups of 200 individuals each. The first group consisted of hypertensive pregnant women and was labelled PIH and the second group consisted of normotensive pregnant women and was labelled Normotensives.

Inclusion Criteria

1. Singleton pregnancy
2. Age below 40 years

Exclusion Criteria

1. Cigarette smoker during pregnancy
2. Habitual alcohol consumer during pregnancy
3. Gestational diabetes
4. Uterine anomaly
5. Obvious placental anomaly
6. Velamentous umbilical cord insertion
7. Multiple gestation
8. Chronic hypertension
9. Sickle cell disease
10. HIV
11. Severe anemia (<8 gm/dl)
12. Fetal congenital anomaly
13. Placenta praevia
14. Chronic liver disease
15. Renal disease

Procedure methodology

After the routine antenatal tests were done, informed consents were obtained from the pregnant women. The blood pressures of the consenting pregnant women were repeated again after an interval of two hours. The results obtained from their blood pressure measurements and urine tests for protein were collected and used to further exclude the pregnant women who gave consent and furthermore, they were recorded as data for this study. The PIH group was made up of women with a blood pressure reading of ≥140/90 mmHg with the presence or absence of proteinuria while the Normotensive group had pregnant women with a blood pressure reading of <140/90 mmHg with the absence of proteinuria. Proteinuria was determined by the use of urine dip sticks.

Ultrasound procedure

Each subject was brought into the ultrasound suite by a female chaperon and appropriately positioned for the procedure. There was a head pillow on the couch to ensure comfort for the subjects. An ultrasonic gel was applied by the Radiologist and with a gentle motion of the transducer on the abdominal surface the fetuses were examined. The fetal anthropometric parameters were measured and these include; Bi-parietal Diameter (BPD), Head circumference (HC), Abdominal circumference (AC) and the femur length (FL). HC/AC ratio was calculated by dividing the value of HC by the value of AC obtained from the measurements of the fetal body parts.

The placenta was examined in both longitudinal and transverse planes to study their echotextures, integrity, edges, substance, basal plates and the chorionic margins. The insertion point of the umbilical cord to

the placenta was determined. The presence of placental calcifications was evaluated by reducing the gain of the ultrasound machine and classified based on the Grannum grading system as follows; [5, 9-13]

Grannum grade 0 presents with a smooth and well-defined chorionic surface, the placental substance is homogenous in echotexture and the basal layer has no echogenic particles. This pattern is commonly noted at gestational ages that are less than 18 weeks.

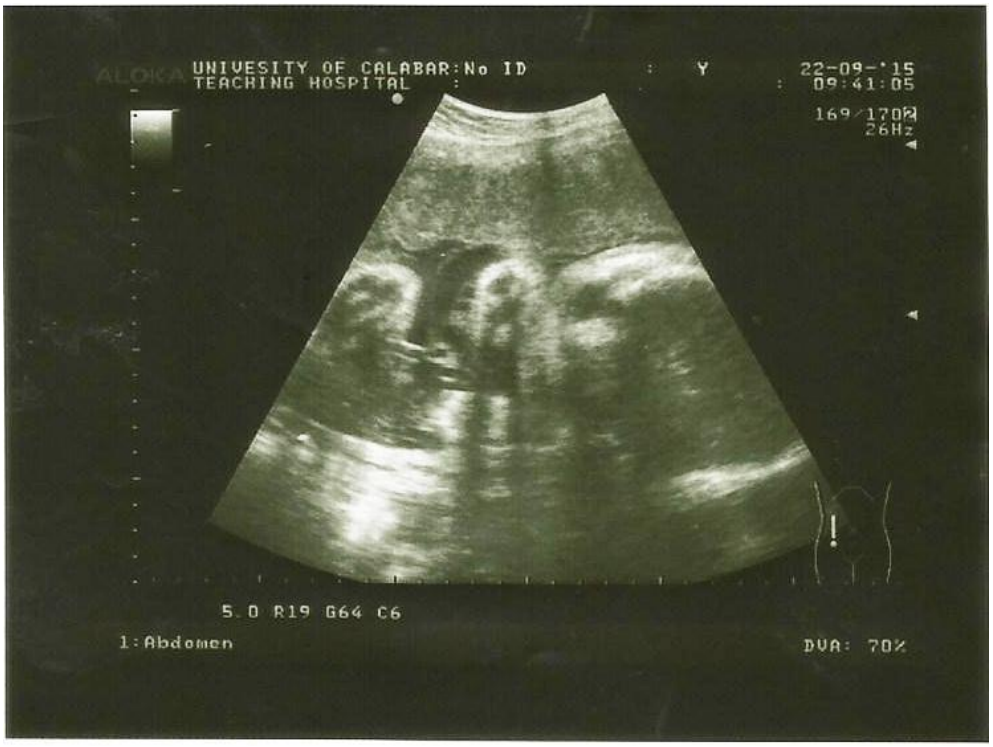

Figure. 1: Grannum grade 0 Placental calcification: Homogenous placenta.

Grannum grade 1 presents with a subtle wavy chorionic plate outline, scattered echogenic particles within the placental substance and no echogenic particle extends to the basal plate. This grade is commonly seen between the 18th to the 29th week of gestation.

Figure. 2: Grannum grade 1 Placental calcification: Scattered bright placental echoes

Grannum grade 2 presents with an obviously indented chorionic plate, linear echogenic particles within the placental substance which lies adjacent the basal plate and produces stippling. This grade is commonly seen from the 30th week of gestation.

Figure 3: Grannum grade 2 Placental calcification: Linear bright echoes parallel to the basal plate of the placenta.

Grannum grade 3 presents with chorionic indentations that extend to the basal plate, large irregular contyledonary-like echogenicities that cast a posterior shadow and large echogenicities within the basal plate. This grade is commonly seen from the 37th week of gestation (term).

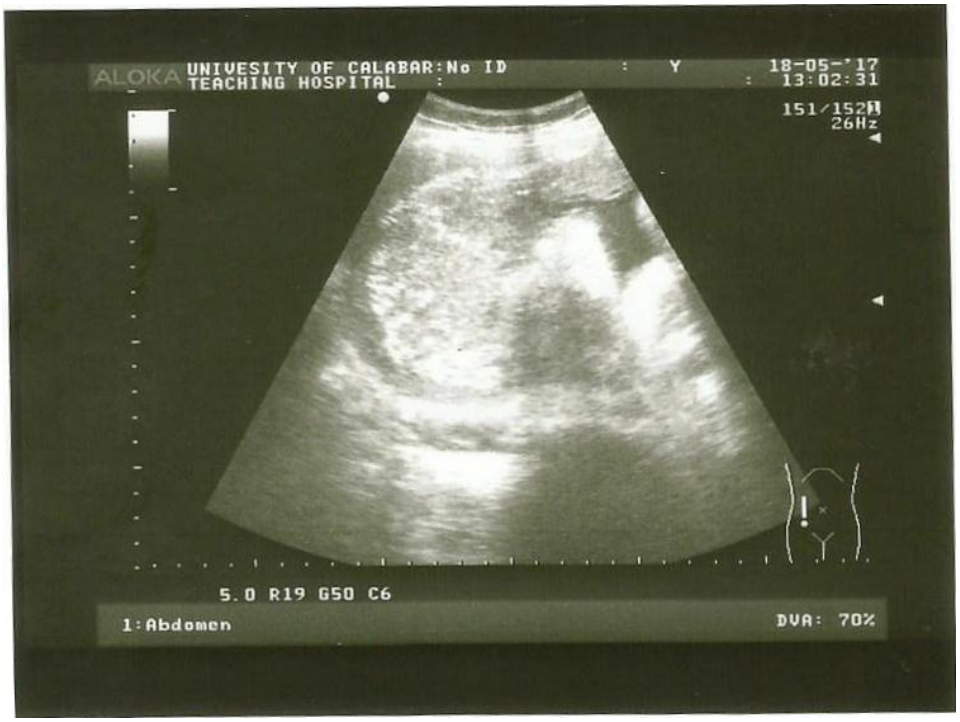

Figure 4: Grannum grade 3 Placental calcification: Calcified cotyledonary septa within the placenta.

The corresponding Grannum grade of placental calcification was recorded for each subject and afterwards the ultrasonic gel was gently cleaned off their abdomen. The subjects were assisted to sit up from the couch by the chaperon and led out of the ultrasound scanning suite.

The ultrasound scan procedures were carried out by 2 experienced Radiologists to rule out intra-observer error and the scanning duration for each subject was approximately 15 minutes. The Ultrasound machine utilized for the study was an Aloka prosound SSD–3500sx (2 Dimensional with Doppler) that has a curvilinear transducer with a frequency range of 3.5-5MHz (manufactured in 2008 by Aloka company limited located in Meerbusch, Germany).

Statistical analysis

The data obtained from the research was analyzed using SPSS version 20 (SPSS Inc., Chicago, IL). Appropriate descriptive and inferential statistical methods were used to analyse the data while tables and charts were the means of displaying the results where applicable. Correlation was determined by using Pearson's correlation P value < 0.05 was considered statistically significant.

III. Result

The age of the subjects was from 16 to 39 years in the PIH while in the Normotensives it was from 19 to 39 years. Figure 5 shows the frequency distribution, in percentage, of the subjects' age in the PIH group.

There were 8 subjects in the 16 – 20 years age subset representing 4% of the PIH group. The 21 – 25 years, the 26 – 30 years, the 31 – 35 years and the 36 – 40 years age subset had 12, 74, 70 and 36 subjects respectively.

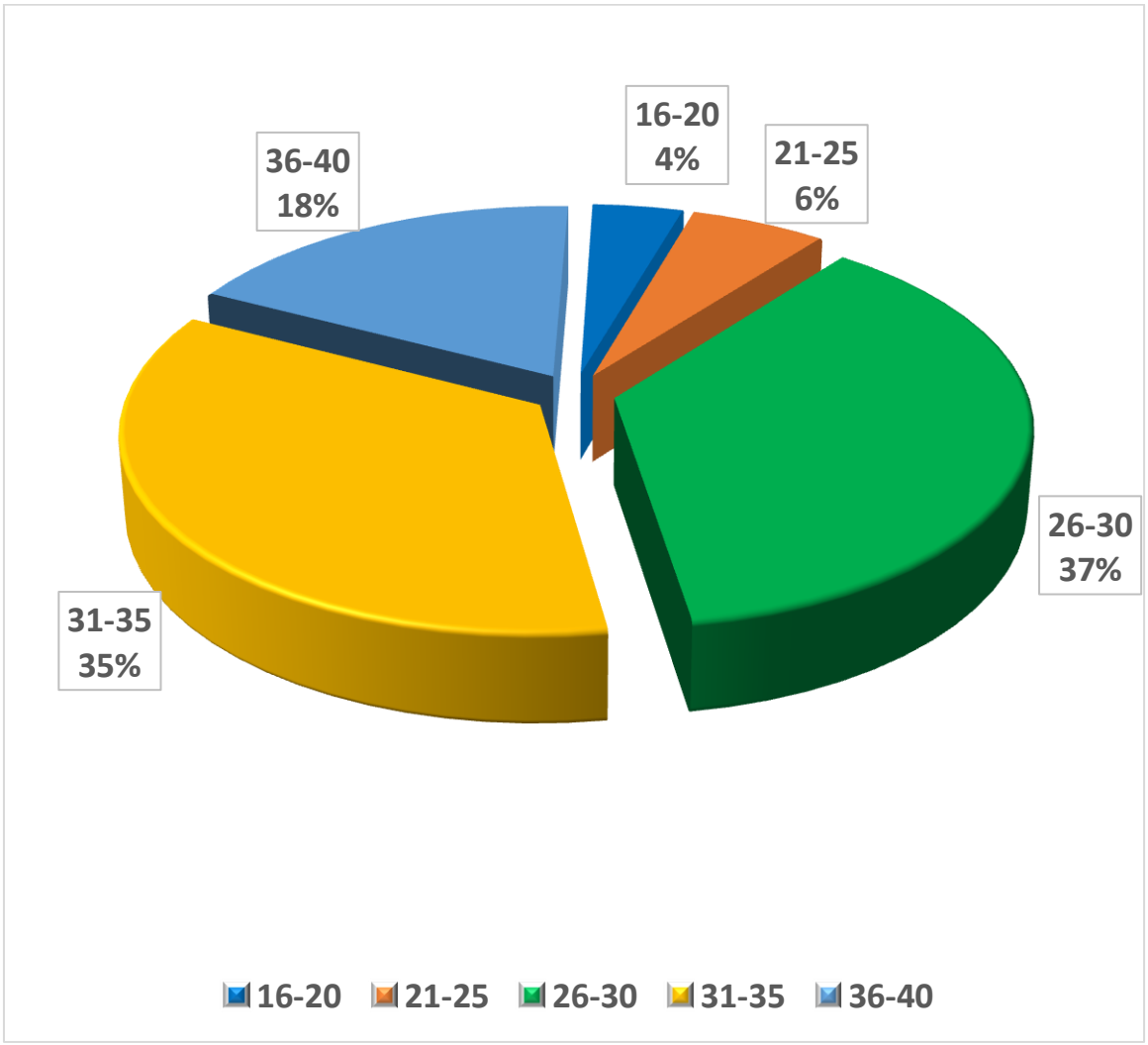

Figure 5: Frequency distribution of age subsets in years in the PIH

Figure 6 shows the frequency distribution, in percentage, of the subjects' age in the Normotensive group.
There were 2 subjects in the 16 – 20 years age subset representing 1% of the Normotensive group. The 21 – 25 years, the 26 – 30 years, the 31 – 35 years and the 36 – 40 years age subset had 28, 84, 58 and 28 subjects respectively.

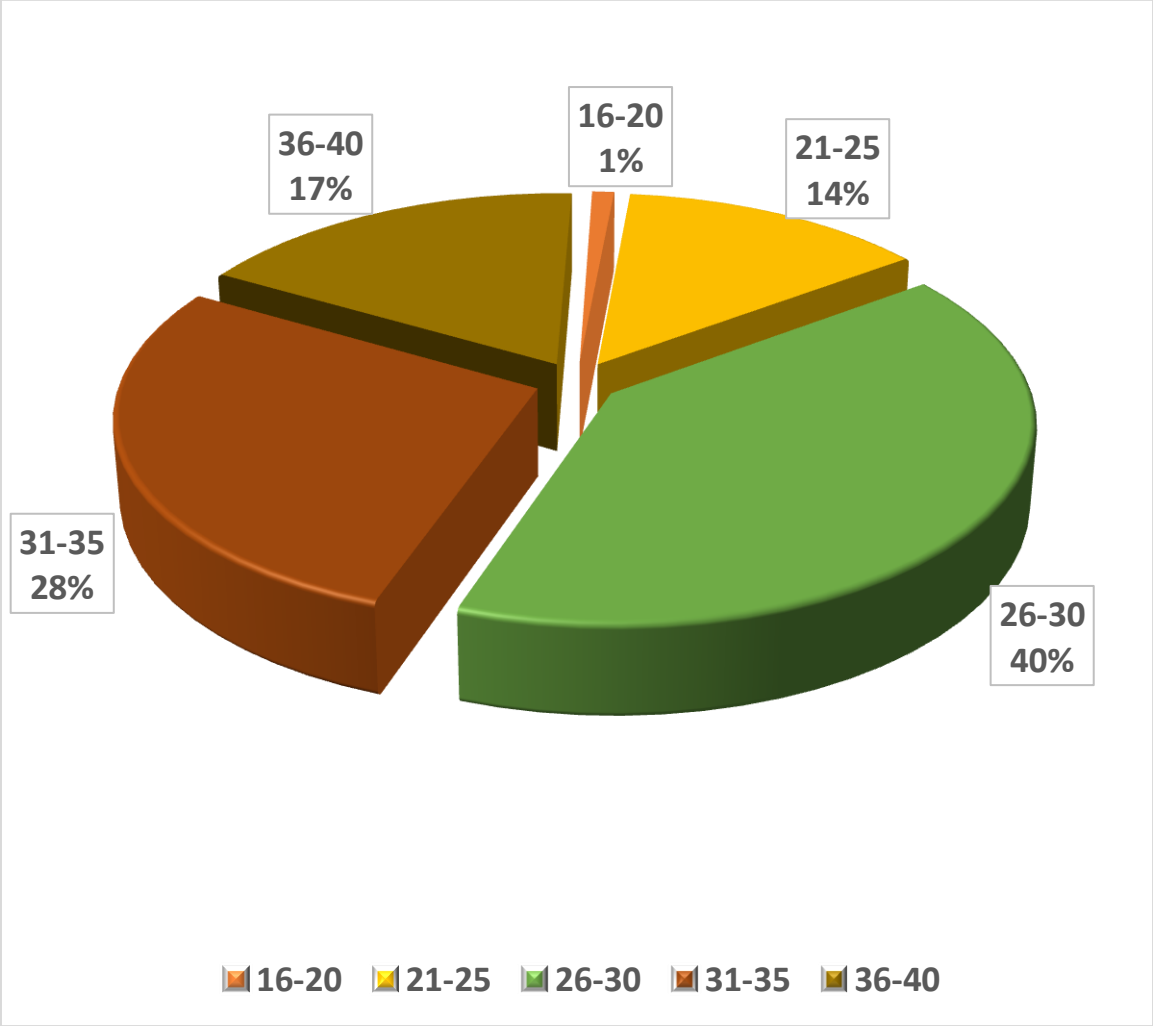

Figure 6: Frequency distribution of age subsets in years in the Normotensives

Table 1 shows the mean, standard deviation and the range of the maternal and fetal variables in the research. The range seen in EFW is 0.38 - 4.38 kg and 0.35 – 4.10 kg in the PIH and Normotensives. The HC/AC had a range of 0.90 – 1.30 in the PIH and 0.90 – 1.20 in the Normotensives.

Table 1: Outlines the key statistics in the PIH and the Normotensives

	PIH				Normotensive			
	n	Range	Mean	STD	n	Range	Mean	STD
EGA (weeks)	200	20.43 – 40.43	32.65	±5.52	200	20.00 – 40.29	32.59	±5.52
EFW (kg)	200	0.38 – 4.38	2.23	±1.07	200	0.35 – 4.10	2.07	±1.02
HC/AC ratio	200	0.90 – 1.30	1.04	±0.07	200	0.90 – 1.20	1.02	±0.07
Systolic Blood pressure (mmHg)	200	140.00 – 280.00	156.93	±21.96	200	100 - 130	112.50	±8.43
Diastolic blood pressure (mmHg)	200	90.00 – 160.00	99.78	±11.42	200	60.00 – 80.00	64.98	±6.53
Proteinuria	200	0.00 – 3.00	0.59	±1.01	200	0.00 – 0.00	0.00	±0.00

Table 2 shows the correlation of the Grannum grades of placental calcification with the different fetal and maternal variables in PIH and Normotensives. EGA, EFW and HC/AC ratio correlated with the Grannum grades in both groups while the systolic blood pressure in the Normotensives also correlated with the Grannum grades.

Table 2: Shows the correlation of the Grannum grades of Placental calcification with the different fetal and maternal variables.

PLACENTAL CALCIFICATION GRADES

		PIH			NORMOTENSIVES	
	n	Correlation coefficient ®	P value	n	Correlation coefficient®	P value
EGA (weeks)	200	+0.546	0.000*	200	+0.420	0.000*
EFW (kg)	200	+0.804	0.000*	200	+0.450	0.000*
HC/AC ratio	200	-0.629	0.000*	200	-0.353	0.000*
Age (years)	200	-0.092	0.195	200	-0.054	0.450
Systolic blood pressure (mmHg)	200	-0.085	0.233	200	+0.150	0.034*
Diastolic blood pressure (mmHg)	200	+0.075	0.294	200	-0.100	0.161
Proteinuria	200	-0.037	0.601	200	-	-

P value <0.05 is significant

Table 3 shows that premature Grannum grade 2 placental calcification was seen in the PIH (22.86 weeks) and the Normotensives (22.00 weeks). The corresponding HC/AC ratio of the premature Grannum grade 2 were 1.10 and 1.10 for the PIH and Normotensives respectively. The other Grannum grades had onsets within the expected EGA.

Table 3: Shows the earliest EGA that each Grannum grade appeared and their corresponding HC/AC ratio measured in the study

PIH				NORMOTENSIVE		
Grannum grades	n	Earliest EGA of Grannum grade appearance (weeks)	Corresponding HC/AC ratio of Grannum grade	n	Earliest EGA of Grannum grade appearance (weeks)	Corresponding HC/AC ratio of Grannum grade
Grade 0	60	20.43	1.20	86	20.00	1.10
Grade 1	36	29.57	1.20	62	22.13	1.00
Grade 2	88	22.86	1.10	48	22.00	1.10
Grade 3	16	35.00	1.00	4	37.43	1.00

Figure 7 shows the variation of the Grannum grades of placental calcification with HC/AC ratio in PIH. Grannum grade 2 placental calcification was noted to have the least HC/AC ratio value while Grannum grade 0 placental calcification had the highest HC/AC ratio value.

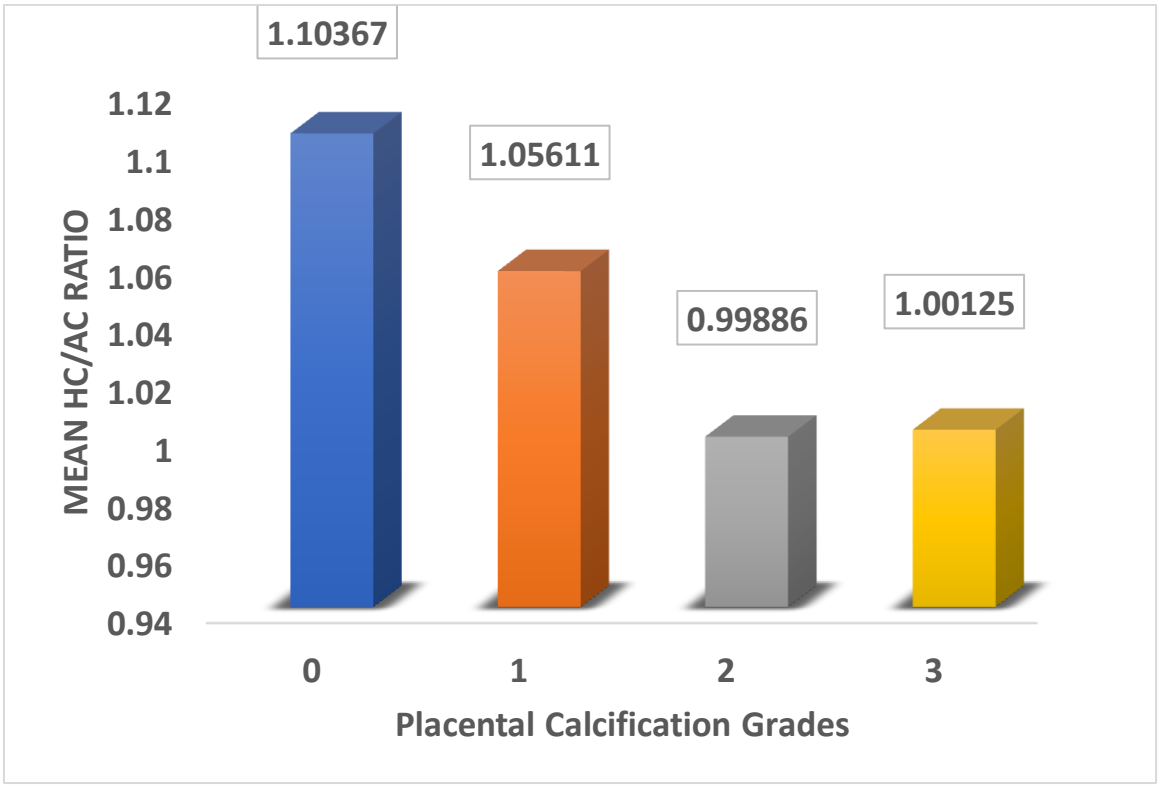

Figure 7: Shows the variation of the Grannum grades of placental calcification with HC/AC ratio in PIH

Figure 8 shows the variation of the Grannum grades of placental calcification with HC/AC ratio in Normotensives. Grannum grade 3 placental calcification was noted to have the least HC/AC ratio value while Grannum grade 0 placental calcification had the highest HC/AC ratio value

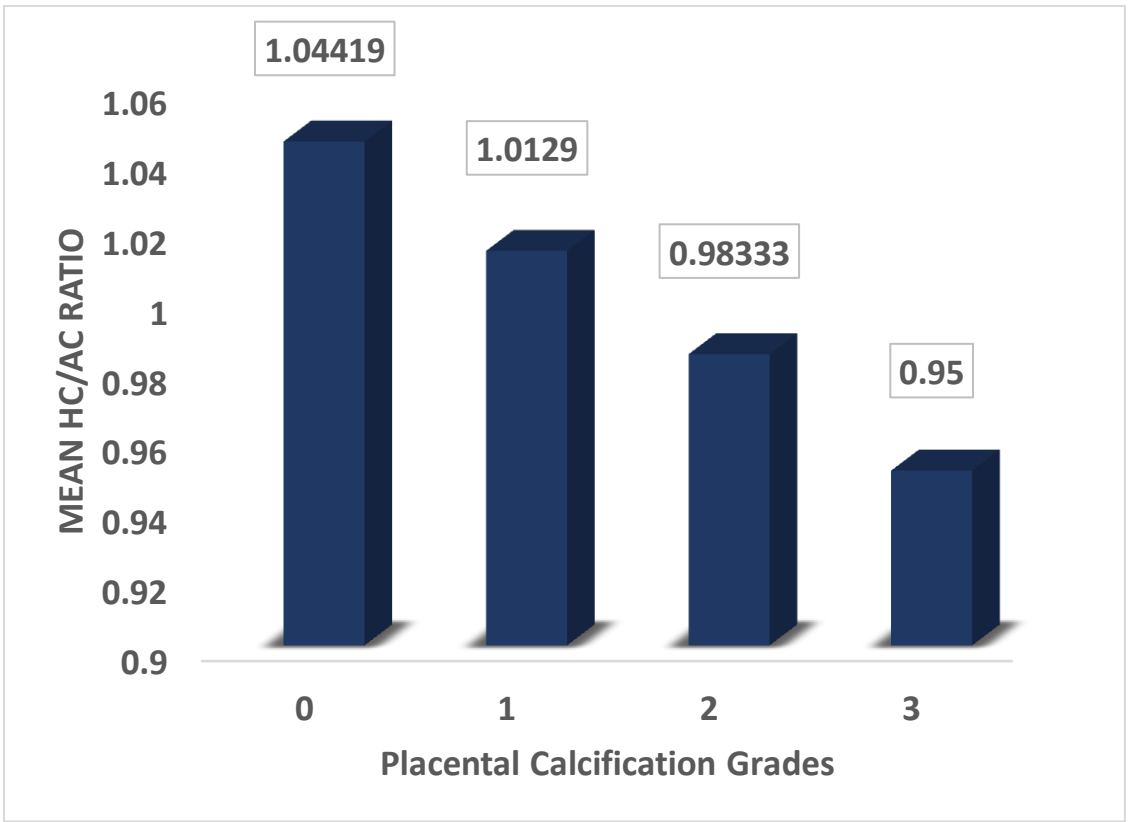

Figure 8: Shows the variation of the Grannum grades of placental calcification with HC/AC ratio in Normotensives.

IV. Discussion

This study demonstrated a significant positive correlation between EGA and Grannum grade of placental calcification (*P* 0.000) in the PIH group and Normotensive group. This is logical because each Grannum grade of placental calcification has gestational age ranges in which it is expected to appear and as the pregnancy progresses the Grannum grades of placental calcification increases from the least to the highest.

We observed that Grannum grades of placental calcification had a significant positive correlation with EFW (*P* 0.000) in both groups which was intriguing and confusing at the same time. Higher grades of placental calcification have been documented as an indicator of fetal weight reduction but the converse was the situation in this study. In contrast, Patterson et al [14] noted in their study that grade 2 placental calcification is associated with lower birth weight but was not associated with poor perinatal outcome. Our study did not exhibit a consistent pattern in the EFW at different Grannum grades of placental calcification. In partial support of Patterson et al, [14] Mirza et al [15] demonstrated that low birth weight and perinatal death are associated with significant placental calcification. However, Miller et al, [16] in a study that involved the examination of 246 placentas within 1 week after delivery found a Grannum grade 3 incidence of 39.4% but no association with birth weight was found.

This study revealed a significant negative correlation between HC/AC ratio and Grannum grades of placental calcification (*P* 0.000) in both groups. A rise in the value of HC/AC ratio above 1.2 [17, 18] implies the existence of asymmetric intra-uterine growth restriction (IUGR). Based on the context of the relationship reported in our study, the premature appearance of lower Grannum grades of placental calcification, and not the highest, are more likely to cause IUGR. Contradicting our observations, Hills et al, [19] in a study where normal and high-risk pregnancies were compared found that intra-uterine growth restriction was associated with higher grades of placental calcification while gestational diabetes and RH sensitization was associated with lower grades. Kazi et al, [20] in a study with 230 term and pre-term pregnancies, it was noted that grade 3 placental calcification is associated with pregnancy complications.

McKenna et al [21] examined 802 low risk pregnancies at 36 weeks and discovered that grade 3 placental calcification assists in identifying growth restricted babies and to predict the subsequent development of proteinuric pregnancy-induced hypertension. Patterson et al [14] also inferred that grade 3 is associated with growth restriction. Miller et al, [16] in tandem with the index study, found that grade 3 placental calcification had no association with impaired fetal growth.

Vosmar et al [22] found a positive correlation between grade 3 which appears before 36 weeks of gestation and fetal growth restriction. In this study it was rather Grannum grade 2 that was culpable of appearing earlier than anticipated in both groups when it was observed before the 23rd week of gestation. It thus, looks like Grannum grade 2 placental calcification has more impact on IUGR occurrence than the other grades do.

Chia et al [7] reported the case of a lady, who in a previous pregnancy 2 years earlier was diagnosed with fetal IUGR and a placenta with severe placental calcification at 27 weeks of gestation and in her current pregnancy Grannum grade 2 placental calcification occurred earlier at 24 weeks and there was also associated IUGR. However, in both instances healthy babies were delivered. [7]

There was no correlation between Grannum grades of placental calcification and blood pressure in the PIH group and in fact, no coherent pattern of relationship was observed in the systolic and diastolic components. In agreement with this finding Patterson et al [14] too did not notice any association between Grannum grades of placental calcification with maternal hypertension. Alemayehu et al [3] inferred that women with PIH had 4.9 times the risk of developing Grannum grade 2 and above placental calcification. Sawant et al [23] also discovered that there were more placentas with higher Grannum grades of placental calcification in mothers with IUGR fetuses compared to mothers with normal fetuses but the difference was not significant. They were of the opinion that the increased calcification noted in the placentas of IUGR fetuses was due to gestational hypertension. [23]

Begum et al [5] interestingly, discovered that PIH was inclined to initiate placental calcification early (P<0.001) and conversely, diabetes had a propensity to delay the calcification of placental tissues. On the other hand, Ezeigwe et al's study [24] demonstrated no significant statistical relationship between the presence of placental calcification in PIH and normotensive pregnant women.

Alemayehu et al [3] found out in their study that the following were significantly associated with Grannum grade 2 and above placental calcification; Educational status, parity, PIH, anemia, smoking and abruptio placenta while Goswami et al [8] noticed that the frequency of placental calcification was high in primigravida. Some of the factors listed like educational status and parity/gravidity were not included for the collection of data in this study. Alemayehu et al [3] furthermore observed that in the cases (PIH) there were 13.2% of placentas with Grannum grade 2 and above. In this study the PIH group that had Grannum grades 2 and above made up 26% of the entire subjects involved while those in the Normotensive group made up 13%.

Meanwhile, Goswami et al [25] discovered in their study that Grannum grades 0 - 3 of placental calcification were seen in 8 placentas of normotensive women while 18 were noted in the PIH group and this

difference was significant. Grannum grades of placental calcification was seen in the placentas of all our subjects in both groups which was not out of place since we evaluated pregnancies between 20 to 40 weeks of gestation.

Donthi et al [26] noted that there were more calcifications in the placentas of pre-eclamptics and eclamptics and the incidence of placental calcification increases as the degree of hypertension increases. Moreover, McKenna et al [21] who examined 802 low risk pregnancies at 36 weeks, discovered that grade 3 placental calcification assists to predict the subsequent development of proteinuric pregnancy-induced hypertension. However, this study demonstrated a negative relationship between the degree of proteinuria and Grannum grades of placental calcification which was not significant (*P* 0.601).

Buttressing the value of placental calcification assessment, Vintzileos and Tsapanov [27] suggested that it should be added as a component of biophysical profile for the ultrasound evaluation of fetal well-being but Chen et al [2] were not in support of the notion and rather advised that more attention should be paid to women who have a grade 3 placental calcification before 36 weeks of gestation even though the pregnancy appears to be normal.

In this study the limitations noted were as follows; Firstly, it was not a longitudinal study to re-evaluate variables that vary with time (blood pressure in particular) in subsequent visits during the study period. Secondly, the researchers did not consider the possible effects of parity/gravidity in this study. Thirdly, fever due to infections such as ones of viral origin, was not included as an exclusion criterion since some infections might be involved in the pathophysiology of placental calcification. [1, 3, 5]

V. Conclusion

The incidence of accelerated placental calcification in pregnancy induced hypertension is double that of the normotensive, though not statistically significant. However, placental calcification is significantly related to the emergence of asymmetrical IUGR and the early appearance of Grannum grade 2 is implicated as a likely trigger for IUGR.

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