Original Research Article

Determinants of calcified placenta and its association with fetal outcome among mothers who gave birth in Southern Ethiopia, 2018

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ABSTRACT

Background: Placenta is a complex multifunctional organ that maintains pregnancy and promotes normal fetal development. Fetal outcome is adversely influenced by pathological changes in placenta because it is a mirror which reflects intrauterine status of fetus. Placental abnormalities are considered as leading cause of maternal and perinatal mortality. Objective of the study was to assess determinants of calcified placenta and its association with fetal outcomes.
Methods: Institutional based unmatched case-control study was conducted on 213 placentas from mothers who gave birth at Dilla university referral hospital with an age range of 19-34 years. Calcifications were assessed radiologically and graded according to Grannum. Bivariate logistic regression analysis was identified and fitted to the multiple logistic regression analysis to identify the independent effects of each variable to the outcome variable. Chi-square test was used to find the potential association between grade two and above levels of calcification and fetal outcomes.
Results: Total 213 singles parturient with their placenta above 37 weeks gestational age were included. The likelihood of developing grade two and above level of calcification associated with the following variables: educational status (OR=3.134; 95%CI: 1.208, 8.135),parity (OR 3.125; 95% CI: 1.354, 7.213) ,maternal anemia (OR 6.834;95%C: I2.626,17.803), smoking (OR 6.343;95% CI: 2.624,15.334), abruption (OR 6.046;95% CI: 2.392,15.277), and pregnancy- induced hypertension (OR 4.868 ;95% CI: 2.095,11.354). In this study, neonatal outcomes in grade II and above level of calcification were poorer than grade I and bellow level of calcification in chi-square association test.
Conclusions: Grade II and above level of placental calcification (case) was significantly associated with maternal pregnancy-induced pathologies, number of parity, maternal educational status, and results in different kind of anomalies, maternal and neonatal mortality. Therefore, the practice of placental examination before and after birth guarantees for feto-maternal wellbeing.

Keywords: Calcification, Grannum, Placenta grade, Radiologic

INTRODUCTION

The placenta is complex multifunctional organs that maintain pregnancy and promote normal fetal development.[1] Fetal outcome is negatively influenced by pathological changes observed in placenta because it is a mirror which revealed the intrauterine status of the fetus.[2] Placental anomalies are the principal cause of maternal and perinatal mortality and important factor affecting fetal growth. Several studies have been conducted in developed countries which have suggested that placental indices have a significant role in fetal growth in terms of weight, body length and cord length.[3,4] Hence, a thorough

examination of the placenta in-utero, as well as post-partum radiologically provides much insight into the prenatal health of the baby and the mother.[5-7] But at this time very little is known about the occurrence of fetal deaths resulting from placenta malformation in Ghana. The allotment of these indices in most developing countries is unfamiliar including Ethiopia.[8-10] Fetal outcome risks due to the different level of maturation (calcification grade) also still unknown in Ethiopia. Therefore, the present study was designed to provide baseline information on determinants of placental calcification and its association with fetal outcome through radiographic assessment.

The aim of this study was to evaluate placental calcification through radiographic examination and identify its main determinants plus how calcification associate with fetal outcomes like intrauterine death, any congenital anomalies, Apgar score, and neonatal death.

METHODS

Study was conducted in the evergreen area of Gedeo zone, Dilla University Referral Hospital, one of the 7 referral teaching hospital in southern region, Ethiopia.

The hospital is located in Dilla city, 360 km to the southeast of Addis Ababa, the capital of Ethiopia. It is one of the largest referral public health institutions in Southern Ethiopia, providing protective, medicinal, and recuperative services to about 1.5 million people in the catchment. It also provides delivery services 24 hours a day, 7 days a week by mid-wives, interns, and obstetricians who assist about 1000-1500 deliveries annually. An institutional-based unmatched case-control study was conducted at Dilla university referral hospital, Gynecology and obstetrics ward from December to July 2018. All full-term placentas following delivery for the duration of eight months were screened for eligibility for the study through radiographic examination and simple inspection.

In this study, specimens were pigeonhole into cases and controls. Cases were placentas with calcification grade levels of ≥2 after radiographic examination; controls were placentas with calcification grade levels of ≤1 after radiographic examination. Cases at this study identified after x-ray interpretation by senior radiologist and for everyone case, two controls were taken.

Sample size determination

In this case, 2 - 4 babies born in each day at DURH. Then total numbers of birth for the entire data collection period were 540 babies which mean 540 placentas were taken. Since this specimen were very small to carry out random sampling, the entire available plus eligible placentas were used.

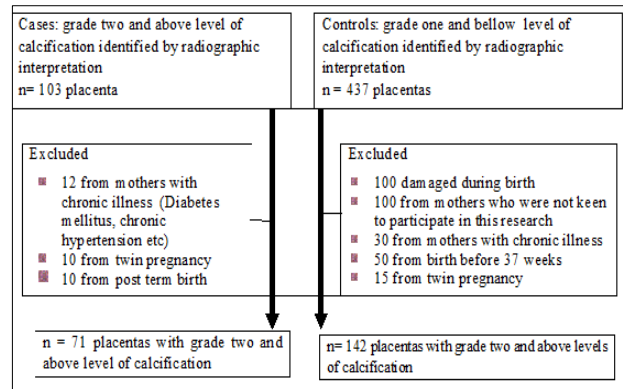Flow diagram describing the exclusion and inclusion of cases and controls of placenta (Figure 1).

Figure 1: Flow diagram of study inclusion.

Data collection tools and procedures

A structured interviewer-based questionnaire was used to collect data on maternal sociodemographic factors, such as age, income, educational, and occupational status. Data on ante partum (parity, smoking, PIH, abruption, anemia), grade levels of placental calcification and neonatal related factors (Apgar scores, existence of congenital anomalies, and stillbirth) were abstracted using a pre-tested structured checklist from the radiographic examination of placenta ,and medical records of pregnant women who gave birth during the data collection period.

The questionnaire was developed based on relevant literature in English but modified to the given context to get the most appropriate data of the participants. The tool has two parts. Checklist was used to retrieve data from the mothers' medical records. Two midwives and two radiographers trained for 2 days collected the data.

The principal investigator and the supervisors inspect the data collection process on daily basis to guarantee data quality and to check for missing information or potential errors. Placental calcification was determined using the 'Grannum grading' system. The grade encompasses four levels as grade zero, grade one, grade two, and grade three. A grade zero signified a placenta was not calcified while grade one signified a placenta with minor calcified but both of the two were all right but a low grade (<2) signified a placenta with more calcified.

Operational definition

Placenta calcification

Deposition of minerals especially around the vessels and allantois due to aging, infarction, and abrasion

Cases

Placenta diagnosed radiographically and having three or more foci of calcification

Controls

Placentas diagnosed radiographically and having two and fewer than two foci of calcification

Excessive calcification

Placenta that had six and above number of foci of calcification.

Inclusion criteria for controls

- All term placentas which had ≤2 foci of calcification with the maternal age range of 19-34 years and parturiate at DURH gynecology and obstetrics ward during the study period.

Inclusion criteria for cases

- A term placenta which had ≥3 foci of calcification with maternal age ranges of 19-34 years as well as parturiate at DURH gynecology and obstetrics ward during the study period.

Exclusion criteria for cases and controls

- Mothers with an age range of 19-34 years but having known chronic diseases and not volunteer to participate in the research as well as post term birth. Placenta destructed during birth or at time of preservation.

Data processing and analysis

Data were entered in SPSS version 23. Followed by checking for any inconsistencies, descriptive analysis was performed. Descriptive statistics, such as means with a standard deviations, frequencies, and percentages were used to describe maternal sociodemographic, ante-partum, grade levels of placental calcification, and neonatal outcomes.

Bivariate logistic regression analysis was done to make a decision whether there is an association between grade two and above level calcification and different factors to select nominee variables for multivariate logistic regression.

Variables with p-values of up to 0.20 in the bivariate logistic regression analysis were identified and fitted to the multiple logistic regression analysis to identify the independent effects of each variable to the outcome variable.

The odds ratio with a 95% Confidence Intervals (CI) was calculated to distinguish the occurrence and strength of associations, and statistical significance was affirmed if p<0.05. Chi-square test was used to find the potential association between grade two and above levels of calcification and fetal outcomes.

RESULTS

Socio demographic characteristics of participants

A total of 213 (71 cases and 141 controls) members were concerned in this study with a response rate of 100%. The mean ages of the parturient of cases and controls were 26.9 (SD=3.4) and 27.0 (SD=3.6) years, respectively. Moreover, 20(28%) parturient of the cases and 18(12.7%) of the controls were daily workers. Twenty-eight (39.4%) parturient of the cases and 24(16.9%) of the controls were illiterate, while one-third (35.2%) of the parturient of the cases and half of (50.8%) the controls had secondary and above level of education. Of the members, 22(31%) parturient of the cases and 40(28.2%) of the controls family monthly income were in the ranges of 2001- 4000 Ethiopian birr (Table 1).

Ante-partum related characteristics

Among the total members, 35(49.3%) of the parturient of the cases and 41(28.9%) of the controls were primiparous ; 26(36.6%) parturient of the cases and 30(21.1%) of the controls had PIH; 26(36.6%) of the parturient of the cases and 32(22.5%) of the controls were smoker during pregnancy; 21(29.6%) parturient of the cases and only 24(16.9%) of the controls had anemia during pregnancy; 19(26.8%) parturient of the cases and 22(15.5%) of the controls had abruption placenta during pregnancy (Table 2).

Placental calcification

The grade two and above levels of calcification among radiographically examined placentas at authors institution was 71/540 (13.2%) (Figure 3) and the rest 469(86.9%) had grade one and bellow level of calcification (Figure 2).

Neonatal outcomes

Out of the total newborn babies, 34(47.9%) of the cases and 95(66.9%) of the control's neonates had Apgar score of more 05 at five minutes while 16(22.5%) of the cases and 31(21.8%) of the control's neonates had Apgar scores of ≤03 at five minutes; 15(21.1%) of the cases and 13(9.2%) of the controls had low birth weight and other minor congenital anomalies. There were 6(8.5%) stillbirth among cases and 3(2.1%) among controls (Table 3).

Determinants of calcification levels of placenta

The bivariate logistic regression analysis showed that maternal age, educational status, occupation, number of parity, monthly family income, PIH, smoking, ANAEMIA, and abruption placenta were associated with grade two and above levels (case) of placental calcification. After adjustments for possible effects of confounding variables, educational status, parity, PIH, smoking, anemia, and abruption placenta were significantly and assertively associated with grade two and above level of placental calcification.

Table 1: Socio-demographic characteristics of the parturient of the cases and controls.

Socio-demographic variables		Cases =71		Controls=142	
		n	%	n	%
Age category in (yrs.)	19-26	39	54.9	98	69.0
	27-34	32	45.1	44	31.0
Level of education	Illiterate	28	39.4	24	16.9
	Grade 1-8	18	25.4	46	32.4
	Grade 9-12	13	18.3	36	25.4
	College diploma and above	12	16.9	36	25.4
Occupation	Employ	17	23.9	33	23.2
	Merchant	11	15.5	34	23.9
	Farmer	12	16.9	35	24.6
	Housewife	11	15.5	22	15.5
	Daily worker	20	28.2	18	12.7
Monthly income (in birr)	<2000	18	25.4	37	26.1
	2001-4000	22	31.0	40	28.2
	4001-6000	11	15.5	46	32.4
	>6001	20	28.2	19	13.4

Table 2: Ante-partum related characteristics of the parturient of the cases and controls.

Ante-partum variables		Cases =71		Controls=142	
		n	%	n	%
Parity	P0	35	49.3	41	28.9
	P1-2	21	29.6	56	39.4
	P3-7	15	21.1	45	31.7
PIH	No	45	63.4	112	78.9
	Yes	26	36.6	30	21.1
Smoking at pregnancy	No	45	63.4	110	77.5
	Yes	26	36.6	32	22.5
Anemia at pregnancy	No	50	70.4	118	83.1
	Yes	21	29.6	24	16.9
Abruption placenta	No	52	73.2	120	84.5
	Yes	19	26.8	22	15.5

The likelihood of developing grade two and above level of calcification among placentas discharged from illiterate mothers were 3 times (OR=3.134, 95%CI: 1.208-8.135) more compared with mothers who had a college diploma and above level of education. Placentas discharged from primiparous were 3 times (OR =3.125, 95% CI: 1.354-7.213) as likely to develop grade two and above level of calcification as those discharged from mothers who gave 4-7 gravidas.

The likelihood of developing grade two and above level of calcification among placentas discharged from anemic, smoker, and abruption case mothers were 6 times (OR=6.838, 95% CI: 2.626-17.803), (OR=6.343, 95% CI: 2.624-15.334), and OR=6.046, 95% CI: 2.392-15.277) more compared with their counter-parts respectively. Placentas discharged from PIH mothers had 4 times higher risk of developing grade two and above level of calcification than those discharged from non PIH mothers (OR=4.868, 95% CI: 2.095-11.310) (Table 4).
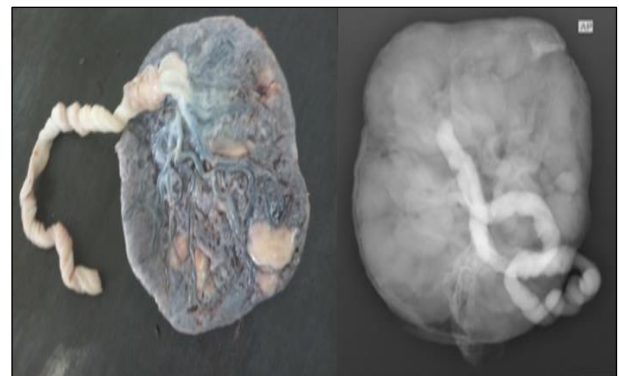

Figure 2: Gross morphology& radiography of normal placenta devoid of calcification, respectively.
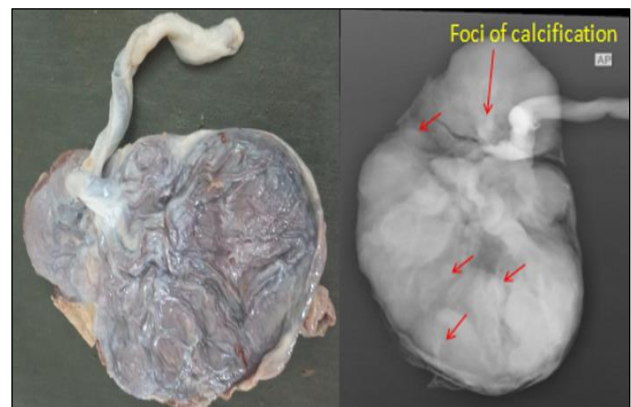

Figure 3: Gross morphology and radiography of placenta with multiple calcifications, respectively.

Table 3: The fetal outcome.

Fetal outcome	Control	Case
Stillbirth	3(2.1%)	6(8.5%)
Any congenital anomaly	13(9.2%)	15(21.1%)
Apgar score 03 or less at 05 minutes	31((21.8%)	16(22.5%)
Apgar score more than 05 at 05 minutes	95(66.9%)	34(47.9%)

Table 4: Bivariate and multivariate logistic regression analysis of factors associated with grade two and above level of calcification, Dilla University referral hospital, Ethiopia, December to July 2018.

Variables		Grade level of calcification		p-Value	Or (95%ci)
		Case=71	Control=142		
Age category in (yrs.)	19-26	39(54.9%)	98(69%)	0.44	1.288(1.016,3288)
	27-34	32(45.1%)	44931%)		1
Occupation	Employ	17(23.9%)	33(23.2%)	0.309	0.628(0.256,1.540)
	Merchant	11(15.5%)	34(23.9%)	0.364	0.666(0.276,1.603)
	Farmer	12(16.9%)	35(24.6%)	0.950	0.971(0.383,2.462)
	Housewife	11(15.5%)	22(15.5%)	0.810	2.157(0.908,5.121)
	Daily worker	20(28.2%)	18(12.7%)		1
Monthly income(birr)	<2000	18(25.4%)	37(26.1%)	0.754	1.131(0.525,2.434)
	2001-4000	22(31.0%)	40(28.2%)	0.108	0.492(0.207,1.169)
	4001-6000	11(15.5%)	46(32.4%)	0.073	2.164(0.931,5.030)
	>6001	20(28.2%)	19(13.4%)		
Level of education	illiterate	24(16.9%)	28(39.4%)	0.019	3.134(1.208-8.135) *
	grade 1-8	46(32.4%)	18(25.4%)	0.585	1.38(0.535-0.580)
	grade 9-12	36(25.4%)	13(18.3%)	0.936	1.042(0.379-2.865)
	>College diploma	36(25.4%)	12(16.9%)		1
Parity	p0	35(49.3%)	41(28.9%)	0.008	3.125(1.354-7.213) *
	p1-2	21(29.6%)	56(39.4%)	0.446	1.405(0.586-3.370)
	P3-7	15(21.1%)	45(31.7%)		1
PIH	Yes	30(21.1%)	26(36.6%)	<0.001	4.868(2.095-11.310) *
	No	112(78.9%)	45(63.4%)		1
Smoking at pregnancy	Yes	32(22.5%)	26(36.6%)	<0.001	6.343(2.624-15.334*
	No	110(77.5%)	45(63.4%)		1
Abruption placenta	Yes	22(15.5%)	19(26.8%)	<0.001	6.046(2.392-15.277) *
	No	120(84.5%)	52(73.2%)		1
Anemia at pregnancy	Yes	24(16.9%)	21(29.6%)	<0.001	6.838(2.626-17.803) *
	No	118(83.1%)	50(70.4%)		1

DISCUSSION

Placental anomalies are leading cause of maternal and perinatal mortality due to placental insufficiency that lead to complications in the fetus.[1,6] A thorough examination of the placenta in-utero, as well as post-partum radiologically provides much insight into prenatal health of the baby and the mother.[3,11]

In the current study, 13.2% of the placenta had grade II and above level of calcification (case) while only 1.7% show excessive calcification. The finding of this study was steady with those studies conducted by Kazzi GM et al, Pushpa Goswami et al, Yaoundé Central Hospital, Cameroon where the frequency of grade two and above level of calcification among placentas were about six to thirty-one.[12-14]

In the current study, efforts were made to make out the determinants of grade two and above level of calcification among placentas at Dilla University Referral Hospital. Educational status, parity, PIH, smoking, anemia, and abruption placenta were identified as determinants of grade two and above level of calcification.

Maternal educational status was an important determinant of placental calcification in this study. Placentas discharged from illiterate mothers were 3 times more likely to develop grade two and above level of

calcification than those placentas discharged from mothers who had college diploma and above level of education. As far as authors searching of articles concerned, there is no other studies which identify maternal education level as determinant factor for the calcification of placenta. But the possible reason for us could be illiterate pregnant mothers most of the time in the study area use anything as they were not conceived especially like 'khat', 'shisha', and other stress inducers which may cause premature calcification of placenta.

Placentas discharged from primiparous had 3.1 times more risk for developing grade two and above levels of calcification. The finding of this study was steady with those of studies conducted in University of Oregon Medical School Hospitals and Clinics by Dr. Fugikura T, Fox H and Faulk WP, Wentworth P, and D. Mckenna et al, where the odds of grade two and above level of calcification among placentas discharged from primiparous were about 3 to 12 times higher compared to placenta discharged from mothers who gave 3-7 gravidas.[15-18]

But other study done on smoker and nonsmoker showed that parity did not influence premature placental calcification in smokers and nonsmokers.[19] However, the difference in the values to some extent may be due to differences in study designs, ethnicity, economic class, and diet especially mothers who are a strict vegetarian.

Placenta discharged from mothers with history of anemia had 6.8 times more risk for developing grade two and above level of calcification. This finding was inconsistent with study done in Indian by Rohini M. et al, showed that anemia has no risk on the development of excessive placental calcification.[3] However, variance in clinical practices /protocols, gestation day, and diet may be the foundation for this divergence and makes a comparison of the results difficult.

Another maternal factor found to have significantly associated with grade two and above level of calcification was smoking. Placentas discharged from mothers who smoke during pregnancy had about 6 times higher risk of developing grade two and above level of calcification. There was comparable result done by Christianson RE, McKenna D et al, University of Alabama at Birmingham Hospital, and Brown HL et al.[18-21] The possible explanation is that smoking induce xenobiotic oxidative stress which increase villous mesenchymal collagen content, trophoblastic membrane thickening, decreased vascularization, villous arteriole edema, and basal plate calcification.[22]

In addition, abruption was important determinant of placental calcification in the current study. Placentas discharged from mothers with history of abruption were 6 times more likely to have grade two and above level of calcification than those discharged from mothers who had no history of abruption. This finding was comparable with study conducted at Liaquat University of medical and health

sciences, Pakistan.[13] This could be explained by the fact that a high proportion of abruption placenta might be caused by retro-placental fibromyoma which might lead to extensive nodules on the surface of the placenta.

Placentas discharged from mothers with history of PIH had 4.9 times more risk for developing grade two and above level of calcification. This finding supported by the study of Dr. Mangal Puri et al, which showed that the majority of the cases with PIH had grade II and III level of calcification, Nahar L. et al, and Salmani D et al.[3,23,24]

The possible reason could be that PIH may operate through several mechanisms such as narrowing umbilical vessels, decrease level of vitamin D on maternal blood.[3]

Neonatal outcomes in grade II and above level of calcification were poorer than grade I and bellow level of calcification in this study as shown (Table 4). Chi-square test was applied as a test of significance and value worked out to be 27.634 which was statistically significant ($p<0.001$). This finding was consistent with those of previous studies conducted by Dr. Mangal Puri et stated that higher grades of placental calcification were associated with bad neonatal outcomes.[3] Other study done by Nigam JS et al, stated that calcification of placenta noted in 66.67 % of low birth weight neonates and 33.33% of normal weighted neonates.[25] However, Patterson et al, stated that grade II is associated with lower birth weight and grade III with growth retardation, but neither associated with maternal hypertension, fetal distress, or perinatal asphyxia.[26] It may be due to calcification changes started at early gestation causing poor uteroplacental flow and result in these entire poor neonatal outcomes.

CONCLUSION

In the current study, the determinants of placental calcification are mainly related to the maternal educational status, parity, PIH, smoking, anemia, and abruption placenta were the determinants of grade two and above levels of calcification. Hence, efforts should be made to get better the quality of antinatal care service, and to identify and construct a stringent follow up of mothers with PIH, anemia, history of abruption placenta, and smokers. Furthermore, thorough examination of the placenta in-utero, as well as post-partum is significant as it provides much insight to the health of the neonates and the mothers.

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