UNIVERSITY OF RWANDA
College of Medicine and Health Sciences
University Avenue
Tel: +250 252530475
P.O. Box 217 Butare, Huye – Rwanda
Fax: +250 252530328
SCHOOL OF MEDICINE

PLACENTAL WEIGHT AND ITS ASSOCIATION WITH MATERNAL AND EARLY NEONATAL CHARACTERISTICS IN SINGLETON PREGNANCIES IN RWANDA

Submitted by: Dr. MANIRAKIZA Emmanuel MD

A dissertation presented in partial fulfilment of the requirement for the Award of a Master of Medicine in Obstetrics and Gynecology

Supervisors: **Dr. RULISA Stephen MD.MPH.PHD.**

Dr. Urania Magriples MD. Associate Professor.

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DECLARATION

I, **Dr.MANIRAKIZA Emmanuel**, hereby declare that, this dissertation entitled ***"PLACENTAL WEIGHT AND ITS ASSOCIATION WITH MATERNAL AND EARLY NEONATAL CHARACTERISTICS IN SINGLETON PREGNANCIES IN RWANDA"*** is my original work and has never been presented elsewhere for academic qualification.

Student Name: Dr.MANIRAKIZAKIZA Emmanuel

Student Number: **214002384**

Sign_____ Date_____

Certification by the supervisor

This research has been submitted with my approval as the Supervisor of University of Rwanda

Name: Dr. RULISA Stephen

Sign_____ Date_____

For and on behalf of University of Rwanda.

DEDICATION

To my wife and my children

To my Parents

To my sisters

To my brothers

To all my Friends and relatives

I dedicate this work

Acknowledgement

I wish to thank the Almighty God who has done a great job throughout my life. I would like also to thank the government of Rwanda, the school of medicine from whom I have gained knowledge and skills of my professional load.

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Acronyms and Abbreviation

AGA : Appropriate for Gestational Age

APGAR: Appearance, Pulse, Grimance, Activity and Respiration.

BW : Birth Weight

CHUK : Centre Hospitariere Universtaire de Kigali

DM : Diabetes Mellitus

GA : Gestational Age

HIV : Human Immunodeficiency Virus

HTN : Hypertension

KDH : Kacyiru District Hospital

NICU : Neonatal Intensive Care Unit

PW : Placental weight

SD : Standard Deviation

SGA : Small for gestational age

Abstract

Objective

To evaluate the relationship between placental weight and maternal complications and short term neonatal outcomes in singleton pregnancies in a Rwandan birth cohort.

Methods

We performed prospective study involving pregnant women and their newborns presenting for delivery at 3 large hospitals in Kigali with singleton pregnancies from 28weeks gestational age over a one year period.

Results

There were 1000 mothers and 1000 babies analyzed during the study period. The mean maternal age was 29.14± 5.90years with the majority being: Multigravida (62.1%) and term (78.8%). Pregnancy complications were present in 31.3%. The mean placental weight was 617.4± 161.63gm with no significant difference between males and females. There was a positive significant correlation between placental weight and birth weight at 37 to 41 gestational weeks in mothers with complications. There was also a significant correlation (r=0.959, p =0.001) at 32 weeks in mother without complications. Low placenta weight/birth weight ratio was significantly associated with poor neonatal outcomes including NICU admission and low Apgars.There was a statistically significant difference in placental weight between stillbirth and healthy babies.

Conclusion:

Placental weight has a strong association with maternal complications and short term neonatal outcomes in Rwanda. Given the lack of availability of pathologic evaluation of the placenta, this simple measurement may aid in the evaluation of perinatal outcomes.

Keyword: Placental weight, Stillbirth, Neonatal outcome

Background

The placenta is an integral part of the maternal fetal unit and is essential for the normal development of the future infant. Its weight at term is approximately 500 gm, and the ratio between placental weight and infant birth weight is approximately1:6.[1]Placental malfunction can result in serious maternal-fetal problems including fetal demise, fetal growth restriction, preeclampsia, and preterm birth. Careful examination of the placenta can provide insight regarding the in-utero environment prior to delivery, and may help explain adverse perinatal outcomes.[2]

The correlation between fetal weight and placental weight is still under investigation. While findings are ambiguous, many studies in different countries have shown the relationship between the placental weight and birth weight and its effect on neonatal outcome. In Nigeria,Abubakal et al. demonstrated that, there is a correlation between placenta weight and neonatal birth weight; however the ratio of placenta to neonatal birth weight at term decreases with advancing gestational age thus, prolongation of pregnancy at term may adversely affect the fetus.[3] Previous studies indicated that high placental weight is associated with poor prenatal outcome, a low APGAR score, respiratory distress syndrome and prenatal death; whereas a low placental weight was associated with maternal medical conditions[4].

A Norwegian study concluded that placental weight is important in determining both fetal development and newborn birth weight, and it also modifies the maternal effect on fetal development and birthweight.[5]The placenta and fetus form from the same genetic origins and certain predispositions in size have a genetic component.[6,7,8]Yu reported that small birth weight reflects a small placental weight with decreased placental tissue function resulting in less perfusion area between mother and fetus, and impaired transfer of oxygen and nutrients from mother to fetus [9]. The results of this study show that fetal growth is regulated by the size and function of the placenta. Heinonen et al. also found that placenta in small-for-gestational-age newborns (SGA) were 24% smaller than in appropriately grown newborns (AGA).[10]Similar findings of smaller SGA neonate placenta compared to those in AGA newborns were reported by Kosinska.[11]

Growing evidence has shown a correlation between placental weight or placental weight to birth weight ratio and short term neonatal outcomes as well as to chronic disease in later life.Kari, et al. conducted a study on the relationship between placental weight relative to birth weight and long-term cardiovascular mortality in over thirty thousand men and women and concluded that a disproportionately large placenta relative to birth weight was associated with increased risk of death from cardiovascular disease. This finding suggests that placental function is important in the association of intrauterine factors with cardiovascular disease later in life.[12]

Birth weights vary widely from country to country therefore placenta weight to birth weight ratio and percentile should be based on data from the actual country or one that is comparable in ethnicity and socioeconomic factors.[13]In current clinical practice in Rwanda, pathological examination and placental weight are not performed. Evaluation of the placenta however may be important to predict neonatal and later adult outcomes and may be an important public health issue in our country. The current study aimed to generate a referral placental weight mean and to examine the relationship between placental weight and maternal related complications during pregnancy and the association between placental weight and short term neonatal obstetric outcomes in singleton pregnancies in Rwanda.

Material and Methods

We conducted a prospective, descriptive and cross sectional study in 3 hospitals in Kigali: (CHUK, KDH and Muhima Hospital) in which a total number of 11,960 mothers consult for delivery per year. The study populations were pregnant women who presented for delivery and their newborns after 28 weeks of GA who agreed to participate in study. Exclusion criteria were pregnant women who consulted for other problems remote from delivery, GA less than 28 weeks, multifetal gestations, suspected or known placental abnormalities requiring hysterectomy, manual or incomplete placental delivery, and intra uterine fetal death before labor, clinical evidence of infection or abruption.

This study used simple random sampling techniques and 5708 pregnant women were registered from March 2016 to September 2016. There were 3204 mothers who did not meet inclusion criteria or refused to participate in study,1405 cases had incomplete data due to missing

maternal or neonatal files and undocumented placental weight were in 99 cases, therefore a thousand mother paired with neonates were analyzed.

A team of trained midwives completed a questionnaire with demographic variables and pregnancy complications (e.g. hypertension, diabetes, HIV, malaria, anemia, Hypermesis gravid alum) were ascertained from medical record review.

Ultrasound examination was performed on admission to determine gestational age and estimated fetal weight, and signs of intrauterine growth restriction. In the absence of a first trimester ultrasound, if ultrasound biometry concurs with menstrual dating, menstrual dates were accepted; if more than 3 weeks difference is noted between menstrual dates and admission ultrasound assessment of gestation age, the admission ultrasound was used to date the pregnancy. Placenta were prepared in the following manner prior to weighing: the membranes were trimmed and the umbilical cord cut at the insertion site on the placenta surface; superficial fetal vessels were drained of all blood and adherent blood clots were removed from the maternal surface. Any gross placental abnormalities were noted.

The birth weight of newborns was recorded to the nearest gram on electronic weighing machine immediately after delivery. APGAR scores were recorded at 1, 5 and 10 minutes. The ratio of PW and BW was calculated and divided into three groups (low, normal, high) PW/BW ratios. Information on birth weight, need for NICU admission and its indication was obtained from the newborn medical record. The stillbirths were not included in the analysis for NICU admission.

Descriptive statistics were performed including mean and Standard Deviation (SD) and frequencies. We used the Spearman Correlation coefficient (r) for assessing the relationship between placental and birth weights and independent sample t test for comparing means of placenta weight within fetal outcome, chi square test was also used for testing the association between placental weight categories and maternal complication during pregnancy and one sample t test for comparison of placenta weight with fetal outcomes and maternal complications. All analyses were done using the Statistical Package for Social Sciences (SPSS version 18.0) for Windows (SPSS Inc., Chicago, IL).

IRB approval was obtained from the University of Rwanda Faculty of Medicine, Kigali University Teaching Hospital, Kacyiru District Hospital and Muhima Hospital ethics committees and patients signed a written consent form in all cases.

Results:

Maternal characteristics are presented in Table 1. The average maternal age was 29.14 ± 5.90 years with 52.2% of the women between ages 26 to 36 years. The mean gestational age was 38.27 ± 2.78 weeks. The majority of pregnancies (78.4%) were term, with 16.9%were preterm 4.7%were post term and 4.9% were stillbirth. The mean placental weight correlates with increasing gestational age as shown in Figure 1. Pregnancy complications occurred in 31.3% of the study population. The majority of women (69.9%) had normal vaginal delivery. The mean of neonatal weight was 3017.90 ± 4.28 gm. The predominance of neonates was not admitted to the NICU (71.3%). (See Table 2). The majority of the placenta weights were normal (79.1%) with only 3.9% being low. The mean placental weight was 617.04 ± 161.63gm.The external assessment of the placenta showed that the majority of pregnancies (77.0%) did not have gross placental abnormalities. The data on placental weights is shown in Table 3.

Placental and birth weight in women with complications from 28 to 43 weeks of gestation are presented in Table 4a. The mean placental weight and birth weight at term increase in a linear relationship. Table 4b compares placental and birth weights in women without pregnancy complications and it also demonstrates a strong correlation at term as well as at 32 weeks ($p = 0.001$) . Table 4c shows that the majority of the study group had a normal placental weight and it highly correlated with birth weight ($p < .0001$) .

A chi-square test of independence was used to compare the frequency of each type of maternal complication within placenta weight categories. HTN, anemia, malaria, and HIV were significantly associated with placental weight. Table 5a demonstrates the significant associations of placental weight to pregnancy complications. The mean placental weights with and without pregnancy complications were significantly different (599.02 vs. 627.20 gm, $p=0.009$)(Table 5b). These differences were more striking with specific pregnancy complications such as HTN and malaria (Table 5c).

The comparison of placental weight and neonatal outcomes are shown in Table 6a.Mean placental weight, NICU admission and low Apgars were associated with low placenta weight. The mean placental weight for stillbirth babies was 541.94 gm and one sample T test demonstrate a

statistically significant difference of 83.56 gm (95% CI, 73.65 to 93.47), $p = 0.000$, between mean placental weight of stillbirths and the mean placental weight of the babies who were not admitted in NICU.

There was also a statistically significant difference in placental weights between the stillbirths and babies with Apgars above seven (89.15 gm, 95% CI, 79.19 to 99.12 gm, $p = 0.000$). Tables 6d and 6e demonstrate that this correlation was present even in women with pregnancy complications though the association was stronger with pregnancy without complications. There was no correlation with infant gender and mode of delivery.

Conclusion

This study demonstrates that placental weight is directly correlated with both maternal complications and adverse short term neonatal outcomes. Placental weights and birth weights from 28 gestational weeks to term increase in a linear relationship and are highly positively correlated in women with and without pregnancy complications. The variability of the correlation at different gestational ages may be due to study population variation or the accuracy of assignment of gestational age.[13,14]The prevalence of HTN was high in the smaller placental weight category which is supported by the literature that all forms of hypertension can be associated with placental insufficiency. Differences with other studies and other countries may be a reflection of varying rates of preeclampsia and hypertension, detection and treatment and timely delivery.[16,17]The low rates of diabetes in our population as well as its treatment may also account for the lack of differences within this subgroup.[18]

The prevalence of malaria, HIV, anemia and Hypermesis was high in high placental weight category and may due to compensatory mechanisms or variability in treatment.[19,20,21] All women with HIV in our cohort were treated with anti-retroviral therefore the disease may have less of an effect on the placental; the mean placental weight in our HIV positive cohort was high ($p<0.0001$).These results differ from that reported by Schwartz, et al. where the mean placenta weight in infected group was 46 gm lower from HIV-uninfected mothers but the difference was not statistically significant.[22] With all the pregnancy complications, we were not able to ascertain adequacy of antenatal treatment and whether this would have implications on placental weight.

In our study, we found that the mean placenta weight to birth weight ratio correlated strongly with short term neonatal outcomes such as admission to NICU and low Apgars. This

finding was seen regardless of the presence of maternal complications which supports the utility of placental weight as a predictor of neonatal outcomes.[23]

Our findings demonstrate that low placental weight is also seen in stillbirth babies which reflects the strong relationship between utero placental insufficiency and low placental weight below 10th percentile, stillbirth and early neonatal death.[24]

Our study is the first in Rwanda documenting a nomogram of placental weight as well as the association between placental weight and maternal and neonatal complications. One of the major limitations of our study is the inability to verify gestational age from the first trimester. This is a real challenge in our setting. Despite this, the placental weight and birth weight data and ratios generated can be used as a reference for our population as measurement of placental weight does not require advanced technology or pathologic review and highly correlates with short term adverse outcomes of the neonate.

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Tables

Table 1: Baseline descriptive characteristics of the study cohort

Demographic items		**Frequency (n=1000)**	**%**
Age category	16-26	354	35.4
	26-36	522	52.2
	36-46	124	12.4
Placental weight	Low (<330g)	39	3.9
Category	Normal(330g-750g)	791	79.1
	High(>750g)	170	17
Period of gestation	Preterm	169	16.9
	Term	784	78.4
	Post term	47	4.7
Gravidity	Primigravida	379	37.9
	Multigravida	621	62.1
Complication during	No	688	68.7
pregnancy	Yes	312	31.3
Mode of delivery	Vaginal delivery	699	69.9
Neonate status	Cesarean Section	301	30.1
	Stillbirth	49	4.9
	Live baby	951	95.1
Neonatal Weight	<2500	166	16.6
Category	2500-4000	796	79.6
	>4000	38	3.8
Sex	Male	500	50
	Female	500	50
Gross Placental	No	770	77
Abnormalities	Yes	230	23

Table 2:Descriptive Statistics for quantitative variables

	Minimum	Maximum	Mean	S.D
Age	16	44	29.14	5.9
GA	28	43	38.27	2.78
One min.APGAR	0	9	7.44	2.14
Five min APGAR	0	10	8.6	2.22
Ten min.APGAR	0	10	9.04	2.16
Fetal Weight	600	4800	3017.9	685.23
Placental weight	120	1480	617.04	161.63
BMI	14.6	47.7	26.67	4.28

Table 3: Mean placental weight in multicenter Kigali city population based on gender and gestational age

Female					Male				
GA	**N**	**Mean**	**S. D**	**Range**	**GA**	**n**	**Mean**	**S.D**	**Range**
28	6	248.17	121.65	120-390	28	8	335.5	125	201-610
29	6	327.17	130.85	130-530	29	2	^		
30	11	408	191.02	170-820	30	2	385.5	133.6	291-480
31	8	467.75	162.401	352-850	31	7	351.71	103.287	120-400
32	9	475.44	195.56	301-878	32	4	455.5	116.5	324-603
33	2	420	141.421	320-520	33	4	487	86.041	345-620
34	9	504.22	57.786	399-600	34	9	528.75	268.037	314-920
35	12	521.67	185.525	240-840	35	13	563.15	176.374	290-845
36	21	626.33	243.451	393-1480	36	18	582.28	159.183	377-960
37	44	622.75	133.351	327-980	37	57	635.34	150.732	340-1080
38	99	630.01	122.787	342-970	38	80	634.68	134.349	382-1004
39	98	644.98	146.624	320-1220	39	126	639.74	120.869	410-940
40	94	633.02	127.299	320-986	40	91	647.24	146.419	301-1020
41	56	657.11	143.668	420-1154	41	55	676.84	156.349	400-1120
42	23	640.09	163.257	355-1036	42	23	678.7	174.071	410-1090
43	2	520	56.569	480-560	43	1	^^		

^ Placenta weight is constant when GA = 29. It has been omitted.

^^ Placenta weight is constant when GA = 43. It has been omitted.

Table 4[a]: Comparison of placental and birth weights at different gestational age (with maternal complication)

		Birth weight (g)		Placenta weight (g)		
GA	**n**	**Range**	**Mean±SD**	**Range**	**Mean±SD**	**r (P)**
28	9	600-1450	940.33±307.096	120-390	244.00±94.481	0.519(0.152)
29	3	700-2300	1320.00±858.604	130-521	321.00±195.655	0.945(0.211)
30	7	700-2450	1516.57±524.889	180-820	477.00±210.809	-0.264(0.567)
31	12	600-2093	1451.75±377.321	120-850	420.92±163.638	0.362(0.247)
32	6	1000-2700	1747.50±610.080	324-710	493.17±141.173	-0.020(0.970)
33	3	1585-2700	2014.00±600.286	314-421	351.67 ±60.119	-0.579(0.907)
34	12	1300-4222	2350.75±1.034E3	345-620	491.50±80.038	0.347(0.269)
35	8	1720-2800	2299.12±337.368	290-730	543.38±169.895	-0.562(0.147)
36	19	1560-3831	2471.26±597.978	377-1480	645.89±253.042	-0.23(0.925)
37	25	2060-3800	2941.44±446.363	327-940	625.92±143.591	**0.453(0.023)***
38	51	805-4521	2970.39±703.657	340-1080	595.10±158.176	**0.502(0.000)****
39	68	2300-4700	3170.34±404.946	320-1000	635.25±144.345	**0.274(0.024)***
40	45	2097-4800	3173.91±562.439	301-986	656.60±155.532	**0.309(0.039)***
41	35	2246-4200	3339.57-464.778	420±1154	699.29±181.823	**0.309(0.071)**
42	8	2800-3700	3197.25±284.661	449±870	639.75±177.225	0.255(0.542)
43	1	Placenta weight is constant when GA = 43. It has been omitted.				

***. Correlation is significant at the 0.05 level (2-tailed)**

****. Correlation is significant at the 0.01 level (2-tailed)**

Table 4[b]: Comparison of placental and birth weights at different gestational age (without maternal complication)

		Birth weight (g)		Placenta weight (g)		
GA	**n**	**Range**	**Mean±SD**	**Range**	**Mean±SD**	**r (P)**
28	5	750-2000	1450.00±543.139	285-610	395.00±127.083	0.598(0.287)
29	5	960-1800	1403.60±352.684	300-530	408.40±113.015	-0.251(0.684)
30	6	900-1900	1286.67±338.802	170-390	320.00±86.429	0.518(0.292)
31	3	1250-1521	1407.67±140.834	357-400	384.33±23.756	-0.634(0.563)
32	7	1325-3087	1903.29±563.323	301-878	448.86±198.135	**0.959(0.001)****
33	3	1954-2800	2284.67-452.223	460-920	633.33±250.067	0.960(0.180)
34	6	1100-2386	1847.67±496.943	390-540	503.83±56.915	0.448(0.372)
35	17	1150-3500	2282.94±660.783	240-845	543.18±187.183	0.173(0.507)
36	20	2100-3900	2858.05±407.038	390-960	568.10±149.285	0.185(0.435)
37	76	2000-4200	3093.14±440.425	410-980	634.45±120.760	0.031(0.793)
38	128	1320-4015	3126.53±413.186	372-1040	647.25±123.067	0.079(0.373)
39	156	1800-4516	3190.46±477.184	340-1220	640.90±137.956	**0.398(0.000) ****
40	140	1600-4800	3269.16±454.245	320-1020	634.69±130.444	**0.478(0.000) ****
41	76	2200-4700	3350.34±452.570	400-1120	651.96±131.065	**0.450(0.000) ****
42	38	1894-4745	3384.92±561.286	355-1090	663.53±168.180	0.177(0.287)
43	2	2230-3730	2980.00±1.061E3	540-560	550.00±14.142	-1(.)******

****. Correlation is significant at the 0.01 level (2-tailed).**

Table4c. **Comparison of placental weight categories and Neonatal weight categories in our study area**

Count		**Placenta weight category**			**Total**
		Low (<330g)	**Normal(330g-750g)**	**High(>750g)**	
Fetal weight	<2500	34	121	11	166
	2500-4000	5	654	137	796
	>4000	0	16	22	38
Total		39	791	170	1000

[r=.326**; P=0.000] **. Correlation is significant at the 0.01 level (2-tailed).

Table 5[a]: Association between placental weight categories and maternal complication during pregnancy

Types of complication	**Placental weight category**				**Chi square**	**P-value**
	<330g n= 39	**330g-750g n= 791**	**>750g n=170**	Total N=1000		
HTN	11(15%)	58(81%)	3(4%)	72	33.291	**0.000***
DM	1(9%)	9(82%)	1(9%)	11	1.188	0.552
Anemia	9(15.3%)	38(64.4%)	12(20.3%)	59	22.848	**0.000***
Malaria	7(11.7%)	44(73.3%)	9(15%)	60	10.291	**0.006***
HIV	1(1.2%)	40(50.7%)	38(48.1%)	79	59.120	**0.000***
Hypermesis gravidalum	2(3.8%)	43(81.1%)	8(15.1%)	53	0.151	0.927

***Association is significant at P< 0.05 level**

Table 5[b]Comparison of placenta weight in pregnancy with complication in general and pregnancy without any complication.

Variables	N	Placental weight (g), Mean±SD	t	P-value
Maternal complication				
No	688	627.20±143.464	**2.615**	**0.009**
Yes	312	599.02±185.789		

Table5[c]Comparison of placental weight in pregnancy with specific complication and pregnancy without any complication.

Maternal Complications	**N**	**Mean**	**Test Value = 627.20**	
			t	**Pvalue**
Hypertension	72	494.15	-8.437	**0.000**
DM	11	593.73	-.729	0.483
Anemia	58	593.40	-1.161	0.250
Malaria	60	550.73	-3.011	**0.004**
HIV	78	714.76	4.643	**0.000**
Hypermesis gravid alum	53	622.25	-.191	0.849

Table 6[a]: The comparison of placenta weight within fetal outcome

Variables	N	Placental weight (g), Mean±SD	t	P-value
Sex				
Male	500	625.23±155.924	**1.363**	**0.173**
Female	500	611.59±160.578		
NICU				
No	687	628.69±127.846	**2.058**	0.040
Yes (Stillbirths)	264 (49)	605.87±204.795		
Mode of delivery				
Vaginal delivery	699	623.19±160.055	**1.454**	**0.146**
C/Section	301	607.32± 153.961		
One Minute APGAR				
<7	302	589.10±200.811		
>7	698	631.09±134.109	**-3.877**	0.000
Five Minute APGAR				
<7	209	594.41±217.76	**-2.470**	0.014
>7	791	624.75±137.930		

Table 6[b]Comparison of mean placental weight for stillbirth and non admitted babies in NICU

	Test Value = 541.94					
	T	**df**	**Pvalue**	**Mean Difference**	**95% CI**	
Mean placental weight not admitted to NICU	16.561	721	.000	83.560	73.65	93.47

Table 6[c]Comparison of mean placental weight for stillbirth babies and above 7 APGAR for the first minute

	Test Value = 541.94					
	t	**df**	**Pvalue**	**Mean Difference**	**95% CI**	
Mean placental weight with babies >7 APGAR	17.563	697	0.000	89.153	79.19	99.12

Table6[d]: Association between the PW/BW ratio and short-term adverse obstetrics outcomes in term newborns without complication during pregnancy period

Variables			PW/BW ratio category		Chi square	P value
			0-0.25	0.25-0.50		
APGAR	At 1st min	<7 N=118	90(76.3%)	28(23.7%)	23.034	0.000
	At 5th min	<7 N=83	58(69.9%)	25(30.1%)	34.441	0.000
NICU	N=100		71(71%)	29(29%)	38.040	0.000

Table 6[e]: Association between the PW/BW ratio and short-term adverse obstetrics outcomes in term newborns with complication during pregnancy period

variables			PW/BW ratio category			Chi square	P value
			0-0.25	0.25-0.50	>0.50		
APGAR	At 1st min	<7 N=67	49(73.1%)	17(25.4%)	1(1.5%)	78.872	0.020
	At 5th min	<7 N=46	30(65.2%)	15(32.6%)	0(0%)	14.959	0.001
NICU	N=58		40(69.0%)	17(29.3%)	1(1.7%)	12.328	0.002

Figure 1: Overall comparison between placental weight mean by Male and Female