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Waist Circumference is a Better Predictor of Recurrent Pregnancy Loss When Compared to Body Mass Index among Nigerian Women

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Abstract
Recurrent Pregnancy loss is a common obstetrics condition with severe physical and psychological consequences to the patients and attending physicians as well. It affects 1-5% of women and up to 50% has no identifiable etiology. Obesity is one of the independent risk factor of this condition; however, the evidence of this association is conflicting. This study aims to further determine that obese women with higher visceral fat are at increased risk of Recurrent Pregnancy Loss. The study was a cross-sectional case-control at a public referral hospital in Kano state Nigeria where 116 women with recurrent pregnancy loss were compared to a comparison control group consisting of 116 normal women. In addition to their socio-demographics, weight, height, BMI, waist circumference, and Hip circumference were collected. It was discovered that Obese BMI range and High-risk value for WC were significantly higher odds of recurrent pregnancy loss (OR, 1.96; 95% CI, 1.37-2.46; OR, 4.61 95% CI, 3.458- 5.696 respectively) Logistic regression analysis showed that the most important factor predicting the occurrence of Recurrent pregnancy loss was waist circumference. The receiver operator characteristic (ROC) curve showed that WC has a considerably higher area under the curve (AUC) and BMI had the least AUC value. This study concludes that waist circumference may be superior to BMI as a risk factor of Recurrent Pregnancy Loss.

Keywords: Recurrent Pregancy Loss, BMI, Waist Circumference.

INTRODUCTION
Recurrent Pregnancy Loss (RPL) as an obstetrics illness with severe psychological complications including, post-traumatic stress disorders, depression, pregnancy-related anxiety, irritability, excessive fatigue, fear, sleep disorders and lack of concentration (Tavoli *et al.,* 2018). It is defined as loss of two or more pregnancies before the 24 weeks gestation affecting 1-5% of all couples. (Aruna *et al.,* 2011; ESHRE, 2017). In addition to its effect on the patients, RPL is equally distressing to clinicians simply because despite a detailed clinical evaluation, no apparent etiology is elicited in up to 40-50% of all cases (Ford and Schust,

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2009; Hong and Marren, 2018). As the etiology remains a mystery, researchers focus on the risk factors of RPL, especially the modifiable ones. Some of the most studied risks of RPL include Obesity, cigarette smoking, excessive use of caffeine, alcohol consumption, advanced maternal and paternal age and family history of miscarriage (Lashen *et al.,* 2004; Boots and Stephenson, 2011; sagiura-Ogasawara *et al.,* 2015).

Obesity is a recognized obstetric risk factor that has been linked to adverse pregnancy outcomes including higher risks of spontaneous and recurrent pregnancy loss (Boots and Stephenson, 2011). One study explained that an obese adolescent has three to fold higher risk of miscarriage and unexplained foetal deaths and even primary infertility in their reproductive life (Polotsky *et al.,* 2010). However, the mechanism to back this relationship is still debated. Since RPL is generally considered a very challenging reproductive health problem, several researchers have made numerous attempts to explain its pathophysiology. The major reason has been the assumption that obesity generally affects female reproduction negatively due to ectopic adipose tissue deposition, greater oxidative stress, and low grade chronic inflammation (Longo *et al.,* 2019). The obese women have also been shown to have Hormonal imbalance involving the Hypothalamus-pituitary hyperactivity (HPA), abnormally high serum LH level with consequent and premature ovulation and luteal phase defects (Leeners *et al.,* 2017).

The great number of obese women with successful reproductive history has puzzled researchers over the years. One big unanswered question is how some obese women get to have successful reproductive life while others do not. This research therefore proposed that obese women with unhealthy visceral fat are more likely to experience poor obstetric outcome. Evidence has shown that visceral obesity in women is of importance and may be the major underlying risk factor for all obesity related complications (Leeners *et al.,* 2017). This is because, in women of reproductive age, estrogen and estrogen signaling generally promotes subcutaneous adipose tissue deposition along the gluteo-femoral region and at the time prevents visceral adiposity (Palmer and Clegg, 2015). We therefore hypothesized that irrespective of BMI; excessive visceral adiposity is a pointer to reproductive dysfunction and may predict higher risk of RPL. The objective of the study was to compare the predictive powers of BMI and other visceral adiposity markers for occurrence of recurrent pregnancy loss. This research will to compare the relative risk of BMI to other measures of visceral adiposity with regards to RPL.

MATERIALS AND METHODS

Study design"

The study was a hospital-based, conducted at Murtala Muhammad Specialists Hospital and Muhammad Abdullahi Wase Teaching hospital in the metropolis of Kano State, Nigeria. The Hospitals are the major referral centers where cases of RPL across Kano State converge to see the specialists. The hospitals are located within the metropolis which is on latitude 12^{o}021N, longitude 08^{o}301E in the north-western region of Nigeria (Fig.3.1) (Ki – Zerbo, 1998). Kano is the most populous state in Nigeria with a population of 9.4 million, and 499 square kilometers Kano state consists of 44 local government areas. The major inhabitants of Kano are of Hausa and Fulani ethnic groups with minorities representing virtually all tribes in Nigeria and a minute fraction of people from the Niger Republic, Ghana, and other nationals. (Dan-Asabe, 1991).

Ethical Consideration
An ethical clearance to conduct the study was obtained from the research ethics committee of the Kano state ministry of health. Informed consent was obtained from each adult participant before.

Participant were women aged 16 to 45 years with two or more previous history of pregnancy loss (RPL) and another group of women who were apparently normal Participants were selected from the Gynecology clinic of the selected hospitals. A proforma was used to record the participant's age, ethnicity, location of birth, and history of miscarriage, and relevant family history.

Variables in the study were socio-demographic characteristics, number of miscarriage, body weight, height, waist and hip circumferences. Participants were selected randomly using the systematic sampling technique with sampling frame of 690 and interval of 2. For the women with RPL, all those patients who were on the RPL were recruited.

Measurements: each patient was privately examined using a mobile hospital screen cover. Height was measured to the nearest 0.1cm as the vertical distance between the standing surface and the vertex of the head with the participant standing upright without shoes using a stadiometer (Price *et al.,* 2006). The weight was measured in kilograms using a digital weighing scale while the subject is in light clothing. The body mass index was calculated using the formula:
BMI= (wt (kg)/ H^2 (m))
Where wt =weight; H = height (Mueller *et al.,* 2004).
Waist circumference (WC) was measured in centimeters with a non- stretchable tape placed horizontally over the abdomen at the narrowest point between the 12^{th} rib and the iliac crest (Lean *et al*., 1995). The hip circumference (HC) was measured while the subject was standing erect with the feet close together. The measuring tape was passed around the point with the maximum protuberance of the buttocks (Hsieh and Yoshinaga., 1999).
The ratio of WC and HC was recorded as waist-hip ratio (WHR).
Abdominal obesity indices were categorized as "normal" or "abnormal" based on the National Cholesterol Education Program (NCEP) reference values. Where WC was considered normal when it <88 cm for females, and WHR was considered normal if <0.85 in females (NCEP, 2002).

Statistical analyses
Bias was eliminated by double blinding where the research assistants who selected participants were not the ones who took the measurement. Each measurement was repeated and the average was recorded to reduce observer error.

The study size involved 116 women with history of RPL and same number of controls.

Data was summarized as mean ± standard deviations of the samples. Chi-square was used to test the relationship between the occurrence RPL with BMI and abdominal adiposity indices (WC, HC and WHR). Pearson's correlation was used to find the relationship between BMI and WC, HC and WHR. Logistic regression was used to evaluate the predictive power of the measured variables SPSS version 26 was used for statistical analyses and $p< 0.05$ was set as level of significance.

RESULTS

In this study it was shown that age was a significant predictor of RP and women age 35 years were more likely to have RPL. Similarly, women whose male partners are aged 45 years and above were more likely to have the condition. Also, women with family history of RPL and excessive intake of caffeine were more likely to have RPL. However no association was observed with tribe and religion as shown in (Table 1)

Also, (Table 2) showed that women with RPL have significantly higher mean BMI, WC, HC, WHR and blood pressure measurements. It was also observed that obese women according to BMI were 1.96 time more likely to have RPL compared to their lean counterparts. Similarly, women with high risk measurement of WC are 4.61 more likely to have RPL compared to those with normal range as shown in (table 3). The cuf off value BMI, WC and WHR above which the risk of RPL was seen to progressively increase was shown to be 27.01, 79.5 and 0.78 respectively as shown in figure 1 and table 4 respectively.

Table 1. Socio-demographic characteristics

Variable		Controls	Cases	$\chi 2$	OR (95% CI)	p-value
Maternal Age (years)	16-34	77	63	3.853	1.8 (1.43-2.03)	0.040*
	>35	40	52			
Paternal Age (years)	Normal	31	19	3.912	1.68 (1.012-4.47)	0.045*
	Advanced	86	96			
Tribe	Hausa	107	94	3.786	0.93 (0.43-2.03)	0.143
	Yoruba	6	14			
	Igbos	3	8			
Religion	Islam	113	105	0.628	0.34 (0.015- 4.12)	0.428
	Christianity	3	11			
Family Hx	NO	112	98	10.043	1.51 (1.10-4.65)	0.002*
	YES	4	18			
Household hx of RPL	NO	116	111	2.519	0.64 (0.15- 3.12)	0.113
	YES	0	5			
Excess Caffeine	NO	112	97	11.287	1.81 (1.2-4.65)	0.001*
	YES	4	18			

Table 2: Anthropometric characteristics of the study participants

	Controls		Cases			
Variable	Mean	Min-Max	Mean	Min-Max	t	p-Value
Wt.(kg)	60.15 ± 11.79	47.9-93.4	63.95 ± 8.75	47.90 - 93.40	1.27	0.021*
Ht(m)	1.58 ± 0.06	1.5-1.79	1.59 ± 0.06	1.47-1.79	0.60	0.548
BMI (kg/m2)	24.89 ± 4.59	15.98-35.58	27.49 ± 3.46	16.98 - 35.59	3.48	0.020*
WC(cm)	79.43 ± 10.25	66-118	86.92 ± 6.63	66-98	3.61	0.010*
HC (cm)	96.44 ± 8.29	78-115	89.95 ± 6.68	79-114	-5.55	0.000*
WHR	0.84 ± 0.06	0.7-1.12	0.89 ± 0.03	0.78 -1.12	6.12	0.000*
NC(cm)	34.01 ± 1.99	31-39.67	35.30 ± 2.12	27- 37	-0.25	0.806
SBP(mmHg)	128.28 ± 12.26	90-160	112.80 ± 8.66	90-130	4.51	0.000*
DBP(mmHg)	69.25 ± 8.56	55-90	72.46 ± 9.52	50-90	10.68	0.000*

BMI: body mass index, WC: waist circumference, HC: hip circumference, WHR: waist-to-hip ratio, NC: Neck circumference DBP: diastolic blood pressure, SBP: systolic blood pressure

Table 3: Relationship between BMI, WC, WHR and RPL

Variable	Categories	Cases	Controls	$\chi 2$	OR (95% CI)	p-value
BMI	Normal	50	44	9.97	1.96 (1.37-2.246)	0.000*
	Overweight	33	66			
	Obese	10	6			
WC	Normal	26	83	31.39	4.61 (4.458-35.696)	0.000*
	High risk	67	33			
WHR	Normal	77	113	14.786	1.09 (0.203-5.858)	0.919
	High risk	16	3			
SBP	Normal	116	81	40.000	0.002(0.000-22.06)	0.239
	Raised	6	35			
DBP	Normal	107	89	1.0580	0.186 (0.023-1.500)	0.304
	Raised	9	27			

BMI: body mass index, WC: waist circumference, HC: hip circumference, WHR: waist-to-hip ratio, DBP: diastolic blood pressure, SBP: systolic blood pressure

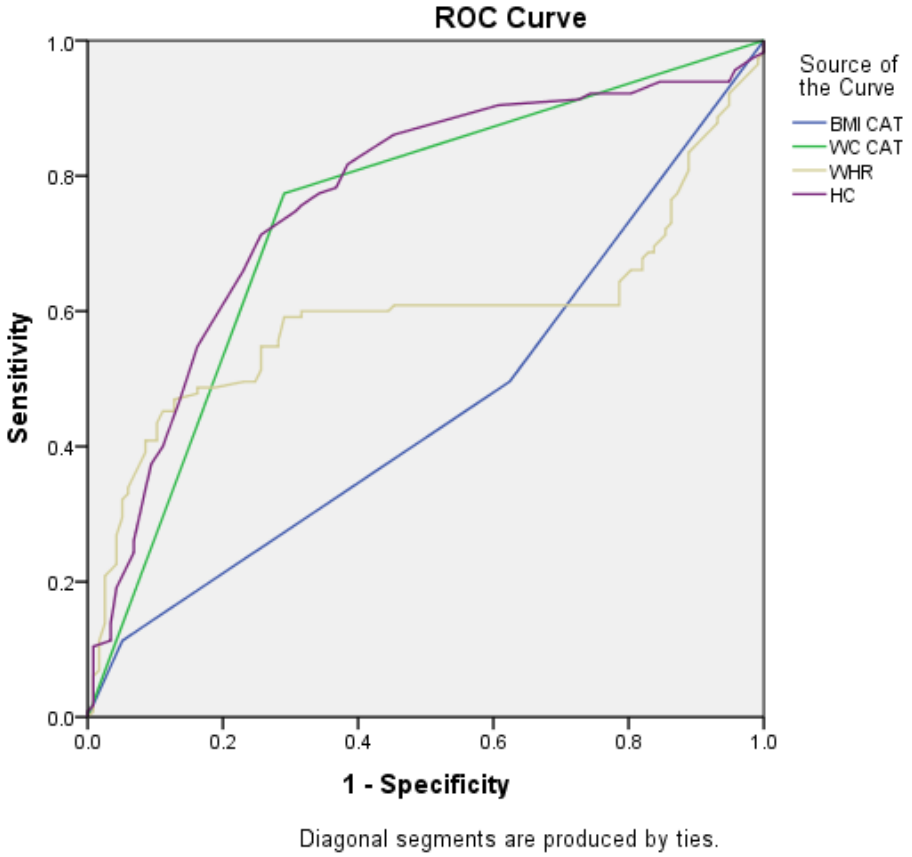

Figure 1. cut off values of BMI, WC, HC and WHR for occurrence of RPL

Table 4: cut off values of BMI, WC, HC and WHR for occurrence of RPL

Variable	AUC	Std. Error	Sig.[b]	95% CI					
				Lower	Upper	cut off	sensitivity	specificity	YI
BMI	0.438	0.041	0.123	0.357	0.519	27.01	0.759	0.241	1
WC	0.708	0.039	0.000	0.632	0.784	79.5	0.891	0.724	1.615
HC	0.745	0.036	0.000	0.677	0.816	82.11	0.75	0.379	1.129
WHR	0.649	0.062	0.102	0.527	0.771	0.78	0.859	0.621	1.48

BMI: body mass index, WC: waist circumference, HC: hip circumference, WHR: waist-to-hip ratio

DISCUSSION

The finding in study that advanced maternal age were significant predictors of RPL is similar to what was documented in the literature by (Nybo-Anderson *et al.,* 2000; du-Fossé, *et al*. 2020 and Frick, 2021). The reason behind this risk was been shown to be the progressive loss of DNA integrity in both males and females (Zhu *et al.,* 2005; Ozawa *et al.,* 2019). Similarly, high caffeine intake was equally shown to be a significant predictor of RPL in previous studies (Pollack *et al.,* 2010). Likewise the positive family history of RPL which generally suggest genetic predisposition (Woolmer *et al.,* 2020).

The findings in this study clearly suggested the mean BMI was significantly higher among women with RPL compared to the normal ones (Table 2). When categorized according to the WHO classification of BMI, BMI was found to be significantly associated with RPL and those with obese range of BMI are 2 times more likely to have RPL compared to lean individuals. This finding is similar to what was obtained by Lashen *et al*, (2004) when they reviewed clinical data from over 16,000 women and concluded that women with an obese range of BMI are 20% more likely to have RPL compared to overweight, normal-weight individuals (3.5, 95% CI 1.03–12.01 P = 0.04). Additionally, a systematic review by (Boots and Stephenson, 2011) of over 28,000 women in the United States revealed that the odds of RPL among the obese were almost 4 folds compared to the normal weight individuals (OR: 3.51; 95% CI, 1.03 to 12.01). In a somewhat varied result, Metwally *et al*, (2010) showed that extremes of BMI i.e. obese and underweight are collectively at increased risk of RPL compared to normal and overweight individuals. However, they equally stressed the role of an obese range of BMI to approach 4 folds (OR-3.98; 95% CI, 1.06–14.92). While stressing the higher chance of repeat miscarriage among the Asian population, Lo *et al*, (2012) equally stated that the risk of RPL among the obese was significantly higher than lean women by (OR 1.73; 95% CI 1.06 – 2.83). A more recent data showed that RPL exclusively related obese BMI range with (OR, 1.75; 95% CI, 1.24–2.47; P = 0.001) (Cavalcante *et al.,* 2019).

Although, these studies have consistently proved that the obese range of BMI is indeed an established risk factor for RPL, the reason behind it is still debated. Li *et al*, (2000) conducted an in-depth risk assessment analysis among obese women with RPL and discovered that 8% had raise serum LH levels, which predispose them to premature LH surge and ovulation of poor quality oocytes and hence poor quality embryos' that would be eventually miscarried. Also, 7.8% were found to have evidence of PCOS. The study also found that free androgen index (FAI) which a ratio of total serum testosterone to the sex hormone-binding globulin (SHBG) was equally elevated in about 14.6% of obese women with RPL. Another finding of the study was low mid-luteal phase progesterone among 17.4% of patients, poorly developed endometrium among 21.1%. (Li *et al* 2000).

Another study concentrated on the role of endometrial dysfunction as a sole reason for higher risk of RPL among obese women and it was concluded that obesity promotes endometrial dysfunction by influencing some major protein expression such as beta globulin and transthyretin (Metwally *et al* 2014). While it has commonly believed that endocrinological and endometrial abnormalities are present in about a quarter of women with unexplained recurrent miscarriage. However, abnormal prolactin, thyroid hormones, and aneuploidy have been ruled out as the main reason behind the increase RPL among obese women (Li *et al.,* 2000; Boots *et al.,* 2014).

This study also found that women with RPL have significantly higher mean value of waist circumference (WC) and waist-hip ratio (WHR). Also Women with a high-risk range of WC were found to have almost 4 fold higher odds RPL compared to those with normal range (table 2). Additionally, Receiver Operator characteristic (ROC) curve showed that WC has considerably higher area under the curve (AUC) and BMI had least area value. Despite the WHO declaration that increased WC poses a relatively higher health risk in obesity compared to BMI, no previous study has shown a clear relationship between RPL and WC. Increased visceral fat in women is a pointer to multiple systemic anomalies that can potentially affect the pregnancy outcome. For instance, in Warming *et al.,* (2003), visceral fat is correlated to the endometrial thickness and free androgen index (FAI) (Nielsen *et al.,* 2007). Visceral at is also associated with increased FSH level and glutathione peroxidase

activity which leads to accumulation of free radicals and oxidative stress in the reproductive system (Klisic *et al.,* 2018). Leeners *et al.,* (2017) have shown that raised visceral fat in women is a pointer to abnormal serum estrogen or estrogen receptor signaling and either one may have a significant impact on a woman's reproductive health. Women with increased visceral fat tend to have diminished levels of sex hormone-binding globulin and a low level of free 17 beta-estradiol and testosterone ratio signifying androgenicity, owing to the elevated levels of free testosterone (Leenen *et al.,* 1994). Women with higher FAI and higher free testosterone have been shown to have a higher risk of RPL (Okon *et al.,* 1998).

CONCLUSION

This study has shown that while obesity is a significant risk factor and predictor of RPL among the study participants, measures of visceral adiposity have more predictive power for RPL and may be used to screen those women and risk. High value of WC and WHR May be considered as potential modifiable risk factors of RPL.

This study recommended that clinicians should consider visceral adiposity assessment in predicting risk of RPL. Also, physical therapist should focus more attention to loss of abdominal obesity for those women who engage in weight loss activity in hope of future pregnancies since it is easier to be lost through exercise.

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