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Reproductive function in premenopausal African Blacks with metabolic syndrome: Associations among inhibin B, adipokines, pituitary and sex hormones and sex hormone binding globulin

O. I. Famuyiwa[1], D. P. Bitrus[1], M. A. Charles-Davies[1]*, U. A. Fabian, A. A. Fasanmade[2], J. A. Olaniyi[3], O. E. Oyewole[4], M. O. Owolabi[2], J. R. Adebusuyi[5], O. Hassan[5], B. M. Ajobo[6], M. O. Ebesunun[7], K. Adigun[8], K. S. Akinlade[1], S. U. Okoli[1], O. G. Arinola[1] and E. O. Agbedana[1]

[1]Department of Chemical Pathology, College of Medicine, University of Ibadan, Ibadan 200284, Oyo State, Nigeria.
[2]Department of Medicine, College of Medicine, University of Ibadan, Ibadan 200284, Oyo State, Nigeria.
[3]Department of Haematology, College of Medicine, University of Ibadan, Ibadan 200284, Oyo State, Nigeria.
[4]Department of Health Promotion and Education, College of Medicine, University of Ibadan, Ibadan 200284, Oyo State, Nigeria.
[5]Medical Social Services Department, University College Hospital, Ibadan 200212, Oyo State, Nigeria.
[6]Dietetics Department, University College Hospital, Ibadan 200212, Oyo State, Nigeria.
[7]Department of Chemical Pathology, College of Health Sciences, Olabisi Onabanjo University, Ago-Iwoye 120005, Ogun State, Nigeria.
[8]General Out Patient Unit, University College Hospital, Ibadan 200212, Oyo State, Nigeria.

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Reproductive dysfunction is associated with metabolic syndrome. Since fertility is highly valued in Africa, preliminary data on the association of metabolic syndrome with indices of reproductive function in premenopausal Nigerian women was provided. Sixty six premenopausal participants (44 with metabolic syndrome and 22 controls) aged 18-45 years were purposely selected for this study. Reproductive history, blood pressure and waist circumference were obtained by standard methods. Fasting blood was obtained for pituitary hormones, adipokines, sex hormone and sex hormone binding globulin, and inhibin B assays by EIA, ELISA and electro-chemiluminiscence. Plasma glucose, triglycerides and high density lipoprotein cholesterol were estimated by enzymatic methods. Free androgen index and oestrogen-testosterone ratio were calculated. Data obtained were statistically significant at *P*<0.05. All reproductive factors except follicle stimulating hormone and free androgen index levels were similar in both groups (*P*>0.05). Leptin levels were higher while adiponectin levels were lower in MS group than controls (*P*<0.05). Reproductive function appears sustained in MS. However, altered adipokines may relate to MS.

Key words: Fertility, leptin, adiponectin, cardiovascular disease, type 2 diabetes mellitus.

INTRODUCTION

Fertility is particularly valued in Africa and the stigma of childlessness is quite profound (Nieuwenhuis et al., 2009; Oladokun et al., 2009; Van der Spuy, 2009). Infertility affects 10% of married couples in Africa and low resource

setting, particularly sub-Saharan Africa, which has the highest prevalence (Noreh et al., 2009; Sharma et al., 2009; Haws et al., 2010). Infection is a frequent cause and an important predictor of infertility in Africa (Dhont et al., 2010). However, the association of non-communicable causes of infertility with reproductive dysfunction has overriding implications (Pembe and Abeid, 2009).

Obesity is described as the worldwide epidemic (Metwally et al., 2008). The MS, characterized by abdominal obesity and insulin resistance, is of global concern and defined as a cluster of interconnected factors that increase the risk of developing CVD and T2DM (Kassi et al., 2011). Now prevalent in Africa and associated with the female gender, the MS can cause disorders of female reproduction, high incidence of menstrual dysfunction, anovulation and infertility in obese women of reproductive age. 44.5% prevalence of MS, with abdominal obesity as the most frequent MS component was recently reported among apparently healthy women in Nigeria (Nasreddine et al., 2012, Charles-Davies et al., 2014).

Leptin and adiponectin are adipocyte-derived hormones. Elevated leptin levels reflect increased adiposity in individuals with MS, being higher in premenopausal women than controls (Fabian et al., 2011; 2015). Hypoadiponectinemia is associated with obesity particularly visceral fat accumulation, insulin resistance and MS. Adiponectin levels vary little during the menstrual cycle (Hall et al., 2009). Its involvement in oocyte maturation, granulosa cell proliferation and death as well as modulator of oestradiol and progesterone secretion has been suggested (Maillard et al., 2003; Dharia et al., 2004; Chabrolle et al., 2009; Papacleovoulou et al., 2009).

Oestrogens are the primary female sex hormones, which readily diffuse across the cell membrane and bind to SHBG. In the theca interna cells in the ovary, androstenedione is synthesized from cholesterol. 17β-HSD catalyzes the conversion of androstenedione to testosterone while aromatase catalyzes the conversion of both androstenedione and testosterone to oestrone and oestradiol, respectively in the granulosa cells (Nelson and Bulun, 2001).

SHBG is a glycoprotein that binds testosterone and oestrogen, which circulate in blood with higher affinity than albumin and transcortin (Laaksonen et al., 2004; Hammond, 2011). Thus, the bioavailability of sex hormones is influenced by SHBG (Somboonporn and Davis, 2004). Low SHBG in both males and females with MS has been reported (Maggio et al., 2007). FAI is a surrogate marker for free testosterone and a determinant of abnormal androgen status in women (Rosner et al., 2007; Fraser and Farrokh, 2014). Elevated FSH, reduced testosterone levels and elevated ETR suggestive of increased conversion of testosterone to oestradiol by aromatase in increased adipose tissue has been reported in pre-menopausal women with MS (Fabian et al., 2015).

Inhibin B is a heterodimeric gonadal peptide secreted by granulosa cells of the ovary, negatively regulates follicule stimulating hormone (Grodstein et al., 1994). It acts locally by enhancing follicle development, thus reflecting the reserve of small antral follicle growth (De Pergola et al., 2006). The inhibitory effect of hyperinsulinaemia on normal folliculogenesis and decreased fertility in obese women has been reported and hyperinsulinemia has been associated with aberrant corpus luteal function while the endometrium may be detrimentally affected by high leptin levels and insulin resistance (Agbaje et al., 2007). Granulosa cell activity and follicular production of inhibin B are decreased in obesity (Nasreddine et al., 2012).

There are ethnic differences in WC, an important MS component and most studies in Nigeria focus on the effect of MS on CVD risk. This study therefore aimed to provide preliminary data on the possible association of MS and factors of reproductive function in premenopausal women in Nigerian population.

MATERIALS AND METHODS

Study design

This was part of a cohort study on Risk Assessment of T2DM in individuals with MS in Ibadan, South West Nigeria conducted in the Department of Chemical Pathology, College of Medicine, University of Ibadan, Ibadan. The study protocol was approved by the University of Ibadan and University College Hospital Health Ethical Review Committee (UI/EC/14/0082). Informed consent was obtained from the participants before recruitment.

Participants

A total of 66 premenopausal females with regular cycles aged 18-45 years were purposely selected from 516 apparently healthy female participants of the cohort study, who were unaware of their metabolic status and not on lipid lowering drugs or hormonal contraceptives. The participants were the only premenopausal females in the cohort that fulfilled the inclusion criteria of this study. Forty four females had MS (cases) while twenty two females had normal (BMI) (18.5-24.9 kg/m^2) without any component of MS (control).

Diagnosis of metabolic syndrome

The JIS (2009) criteria were used for the diagnosis of participants

*Corresponding author. E-mail: mcharlesdavies@yahoo.com.

with MS (Alberti et al., 2009). The criteria include any three of the following conditions: elevated WC (80 cm), elevated triglyceride (≥150 mg/dL), reduced HDLC (≤50 mg/L, BP {SBP ≥ 130 mmHg, DBP ≥ 85 mmHg} and elevated FPG (≥100 mg/dL). These parameters have been described elsewhere (Umoh et al., 2010; Charles-Davies et al., 2012)

Sample collection

Ten milliliters of fasting (8-14 h overnight) venous blood samples were aseptically collected by venepuncture from the participants at the follicular phase of their menstrual cycle. 4 mL of blood were dispensed into K_3EDTA bottle for the determination of TC, triglycerides and HDLC. 2 mL of blood were dispensed into fluoride oxalate tubes for FPG estimation. 4 mL of blood were dispensed into plain tubes and kept for 1-2 h to clot to obtain serum for hormones (testosterone, oestradiol, inhibin B, adiponectin and leptin) and SHBG. All samples were centrifuged at 500 g for five minutes after which plasma and serum were obtained and stored in aliquots at – 20°C until time of analyses.

Reproductive history

Reproductive history- AM, LOMC, DOP, NOP, NLB, NPCT and NA were obtained through semi-structured pretest questionnaire administered to the participants.

Fasting plasma lipids and glucose

Triglyceride, HDLC and FPG were estimated by enzymatic methods (Charles-Davies et al., 2012).

Hormones and sex hormone binding globulin

Leptin, inhibin B, total adiponectin and SHBG were estimated by enzyme linked immunosorbent assay (Diagnostic Automation, Inc., CA; RayBiotech, Inc. USA; Assaypro Human, USA and Cloud-Clone Corporation, USA respectively). Pituitary hormones-FSH, LH and prolactin were estimated by enzyme immunoassay (immunometrics (UK) Ltd). Sex hormones-testosterone and oestradiol were estimated by automated chemiluminiscence technique (COBAS e 411, Roche, Germany) while ETR and FAI were calculated. FAI was calculated as 100×total testosterone/SHBG.

Statistical analysis

Statistical package for Social Science 17.0 was used for statistical analyses. Analysis of covariance was used for comparison of variables, which were adjusted for age while Stepwise multiple regression model was used to find relationships. Data obtained were significant at P <0.05.

RESULTS

Table 1 shows comparisons of age, MS components and reproductive history between the cases and controls (after age adjustment). All MS components except TG were significantly different between cases and controls (P<0.05). WC, BP and FPG levels were significantly higher while HDLC was significantly lower in cases when compared with control (P<0.05). The reproductive history of cases showed no significant differences between the MS group and controls. However, age was significantly higher in MS groups when compared with controls (P>.05).

Table 2 shows comparisons of hormones and SHBG between cases and controls. Adiponectin was significantly reduced while FAI, leptin and FSH levels increased in cases when compared with controls (P< 0.001). However, inhibin B, SHBG, testosterone, oestradiol and ETR in cases showed no significant differences when compared with controls (P>.05). Age were significantly higher while height was lower in cases than controls (P<0.05).

Table 3 shows multiple regression of hormones/globulins, MS components and reproductive history. DBP had a positive relationship with leptin, SHBG and testosterone in the control group while SBP had a positive relationship with FSH in the cases. Adiponectin had a positive relationship with SHBG and vice versa in the cases only. FAI had positive relationship with testosterone and vice versa in the controls while it has a negative relationship with SHBG and vice versa in the cases. Inhibin B had a negative relationship with SHBG while NPCT had positive relationship with Inhibin B in cases only. AM had a negative relationship with ETR while NOP had a positive relationship with FSH and LH in the controls only. Oestradiol and testosterone had a positive and negative relationship with ETR respectively and vice versa in both controls and cases. These relationships were all significant (P<0.05).

DISCUSSION

MS is a complex disorder that is considered a worldwide epidemic (Christian, 2012). Obesity associated with MS has been associated with disorders of female reproduction, high incidence of menstrual dysfunction, anovulation and infertility in obese women of reproductive age (Nasreddine et al., 2012). Hyperinsulinaemia, a characteristic of MS has been shown to inhibit normal folliculogenesis, decreasing fertility in obese women (Agbaje et al., 2007). De Pergola et al. (2006) demonstrated reduced LH, FSH, Inhibin B and oestradiol in overweight and obese women suggesting defective folliculogenesis.

Contrarily, the present study showed similarity in the indices of reproductive history between cases and controls (P>0.05). Inhibin B is widely used as a surrogate marker of folliculogenesis (Agbaje et al., 2007). Childbearing has been linked to the high incidence of MS among women of reproductive age (Gunderson et al., 2009). Similar Inhibin B levels were observed in cases and controls in this present study (P>0.05). NPCT was

Table 1. Age, metabolic syndrome components and reproductive history in premenopausal women with and without metabolic syndrome.

	MS (n= 44)	Controls (n= 22)	t	*P*
Age (years)	39.2±5.4	28.7±6.2	7.1	< 0.001*
MS component				
WC (cm)	101.9±10.9	75.9±4.6	10.7	< 0.001*
SBP (mmHg)	142.8±24.9	113.2±7.8	5.4	< 0.001*
DBP (mmHg)	89.6±12.8	71.8±4.0	6.3	< 0.001*
TG (mg/dL)	64.5±27.8	59.6±29.1	0.7	0.509
HDLC (mg/dL)	35.2±9.6	56.9±9.4	-8.7	< 0.001*
FPG (mg/dL)	103.1±44.5	79.2±8.5	2.5	< 0.015*
Reproductive history				
AM (years)	16.2±2.0	15.1± 2.3	1.9	0.670
LOMC (days)	29.4±3.0	29.6±3.0	-0.3	0.731
DOP (days)	4.8 ±1.5	4.7± 0.9	0.2	0.817
NOP	4.6 ±1.8	3.4±2.1	2.0	0.053
NPCT	4.1± 1.5	3.0±1.9	2.0	0.061
NA	3.7±1.3	2.7±1.7	2.2	0.052

Values in mean ± SD , t= student t-test; p= probability, *= significant, n= number, TG=triglyceride, HDLC=high density lipoprotein cholesterol, cases= premenopausal women with metabolic syndrome, controls=premenopausal women without metabolic syndrome, MS Components= metabolic syndrome components, SBP=systolic blood pressure; DBP=diastolic blood pressure, FPG=fasting plasma glucose, AM=age at menarche, LOMC=length of cycle, DOP=duration of period, NOP=number of pregnancies, NPCT=number of pregnancies carried to term, NA=number of children that are alive.

Table 2. Hormones and sex hormone binding globulin in premenopausal women with and without metabolic syndrome.

Hormones/globulin	Cases (n= 44)	Controls (n= 22)	t	*P*	RI
Inhibin B (pg/mL)	215.0±188.2	249.1±180.1	-0.7	0.454	> 139
Adiponectin (ng/L)	25.5±10.6	40.5±8.8	-4.8	< 0.001*	3.5-22.4
Leptin (µg/L)	28.9±26.4	11.4±7.4	2.7	<0.011*	3.63-11.09
LH (IU/L)	19.8±19.0	12.3±7.2	1.7	0.086	1.6-9.6
FSH (IU/L)	24.4±29.0	10.6±13.1	2.1	0.042*	3.3-12.9
Prolactin (mIU/L)	448.9±391.4	840.0±1205.6	-2.0	0 .054	78-455
Testosterone (nmol/L)	2.2±1.9	2.1±1.6	0.3	0.665	0.7- 2.8
Oestradiol (nmol/L)	0.2±0.1	0.4±07	-1.7	0.882	0.07-0.6
SHBG (pg/mL)	90.5±58.5	101.0±43.6	-0.8	0.987	40-120
ETR	0.2± 0.2	0.2±0.2	0.0	0.973	-
FAI (%)	5.9±9.3	2.6±2.1	1.6	<0.001*	-

Values in mean ± S.D., WC=waist circumference, ADP=Adiponectin, FAI=free androgen index, SHBG=sex hormone binding globulin, t= student t-test, p= probability, *= significant; n= number, ^{MS} components=metabolic syndrome components. n for leptin in control and cases= 17 and 30, respectively, LH=luteinizing hormone, FSH= follicle stimulating hormone, ETR=oestradiol testosterone ratio, RI= reference interval, reference intervals are as determined by manufacturer as local reference values are unavailable.

also positively related with Inhibin B in cases only (*P*<0.05). Moreover, similar levels of indices of reproductive function except FSH were also demonstrated between cases and controls in this study (*P*>0.05).

A negative relationship was also demonstrated between AM and ETR in controls only (*P*<0.05) suggesting that women without MS probably have increased exposure to oestrogen. Stockl et al. (2011) reported an association of AM with a higher risk of having

Table 3. Multiple regression of hormones/globulins, metabolic syndrome components and reproductive history.

	Dependent Variable	Predictors	β	t	*P*
Controls					
R^2=0.199, F=5.940, *P*=0.014	Leptin	DBP	0.284	1.649	0.014
R2=0.370, F=8.846, *P*=0.007	SHBG	DBP	0.554	2.974	0.007
R^2=0.641, F=12.781, *P*=0.002	Testosterone	DBP	0.502	3.652	0.002
R^2=0.390,F=16.998, *P*=<0.001	Testosterone	FAI	0.596	4.330	<0.001
R^2=0.390, F=12.781, *P*=0.002	FAI	Testosterone	0.624	3.575	0.002
R^2=0.647, F=36.664, *P*=<0.001	Oestradiol	ETR	0.804	6.055	<0.001
R^2=0.804, F=36.664, *P*=<0.001	ETR	Oestradiol	0.694	5.322	<0.001
R^2=0.850, F=24.654, *P*=0.036	ETR	AM	-0.295	-2.260	0.036
R^2=0.434, F=6.894, *P*=0.028	LH	NOP	0.659	2.626	0.028
R^2=0.765, F=26.071, *P*=0.001	FSH	NOP	0.875	5.106	0.001
Cases					
R^2=0.210, F=11.158, *P*=0.007	Testosterone	ETR	-0.385	-2.823	0.007
R^2=0.493, F=19.912, P=<0.001	ETR	Testosterone	-0.486	-4.363	<0.001
R^2=0.257, F=14.541, *P*=<0.001	Oestradiol	ETR	0.507	3.813	<0.001
R^2=0.257, F=14.541, *P*=<0.001	ETR	Oestradiol	0.533	4.781	<0.001
R^2=0.351, F=17.340, *P*=<0.001	SHBG	Adiponectin	0.485	4.383	<0.001
R^2=0.384, F=21.804, *P*=<0.001	Adiponectin	SHBG	0.620	4.669	<0.001
R^2=0.573, F=20.791, *P*=<0.001	SHBG	FAI	-0.443	-3.976	<0.001
R^2=0.357,F=19.499, *P*=<0.001	FAI	SHBG	-0.598	-4.412	<0.001
R^2=0.650, F=18.568, *P*=<0.001	SHBG	Inhibin B	-0.280	-2.570	0.015
R^2=0.143, F=7.689, *P*=0.008	Inhibin B	NPCT	0.406	2.773	0.008
R^2=0.117, F=5.555, *P*=0.023	LH	FSH	0.342	2.357	0.023
R^2=0.117, F=5.555, *P*=0.023	FSH	LH	0.313	2.247	0.030
R^2=0.212, F=5.513, *P*=0.008	FSH	SBP	0.310	2.225	0.032

ADP=Adiponectin, FAI=free androgen index, SHBG=sex hormone binding globulin, t= student t-test, p= probability and are all significant, SBP=systolic blood pressure, DBP=diastolic blood pressure, AM=age at menarche, NOP=number of pregnancies, cases=women with metabolic syndrome, controls=premenopausal women without metabolic syndrome, MS components=metabolic syndrome, LH=luteinizing hormone, FSH= follicle stimulating hormone, NPCT=number of pregnancies carried to term, ETR=oestradiol testosterone ratio, VAI=visceral adiposity index, WHtR=waist height ratio, R2=Regression coefficient, β=beta coefficient.

MS in Bangladeshi premenopausal women. These findings suggest that MS may not decrease fertility in African black women of reproductive age.

Normal increases in FSH and LH levels in the follicular phase support folliculogenesis. NOP had a positive relationship with FSH and LH in the controls only. Metabolic syndrome is known to increase with age (Charles-Davies et al., 2014). The mean age of the cases was higher (39.2 years) than controls (28.7 years) (*P*<0.05). The increase in FSH levels in the cases compared with the controls (*P*<0.05) may suggest compensatory hypogonadism in the cases. As women approach menopause, FSH levels fall, ovarian follicular activity decreases, leading to decline in oestrogen level (Fabian et al., 2015). There is the resultant gradual loss of hormonal feedback mechanisms leading to the compensatory elevation of FSH for adequate production of oestradiol.

SBP had a positive relationship with FSH in the cases only (*P*<0.05) in this study. Blood pressure is known to increase in MS, with age and with increasing measures of adiposity-known cardiovascular risk factors (Charles-Davies et al., 2013). Moreover, higher FAI, a surrogate marker of free testosterone in cases than controls was demonstrated (*P*<0.05). Andersson et al. (2001) reported an association of increased FAI with cardiovascular risk factors in premenopausal women and was strongly affected by BMI. FAI had positive relationship with testosterone and vice versa in the controls while it has a negative relationship with SHBG and vice versa in the cases (*P*<0.05). FAI concentrations are driven primarily by SHBG abundance and SHBG regulates the availability of biologically active free testosterone and oestrogen, and their metabolic clearance rate. This implies that testosterone excess in women lowers SHBG concentration, with increase in FAI (Rosner et al., 2007). In this study, a negative relationship was observed between inhibin B and SHBG in cases only (*P*<0.05).

DBP also had a positive relationship with SHBG and testosterone in the control group only (P<0.05). Cardioprotective mechanisms are not fully understood (Charles-Davies et al., 2014), However, the cardioprotection of premenopausal women without MS only, has been postulated (Fabian et al., 2015). The possible mechanism may be that SHBG production is stimulated by oestrogen and inhibited by androgens indicating that a high level of SHBG would moderate the unfavourable effects of free androgens on blood pressure (Ding et al., 2006). Testosterone may in addition, contribute to increased blood pressure through the rennin-angiotensin-aldosterone system (Kienitz and Quinkler, 2008). Oestradiol and testosterone had a positive and negative relationship with ETR respectively and vice versa in both controls and cases (P<0.05).

The visceral adipose tissue secretes leptin, an adipocytokine associated with the processes of inflammation, endothelial dysfunction, hypertension and atherogenesis. Increased levels of leptin in cases when compared with controls (P<0.05), observed in this present study has been previously reported (Fabian et al., 2015). DBP had a positive relationship with leptin in the control group only (P<0.05). it was shown that elevated leptin levels might be compensatory to reduce body weight and blood pressure in MS (Fabian et al., 2011, 2015). These findings are contrary to previous report of a link between leptin and reproductive dysfunction (Chou and Mantzoros, 2014).

However, adiponectin, another adipokine with anti-atherosclerotic, anti-inflammatory and antioxidant effects (Mohammed and Mohammed, 2011) was significantly reduced in MS group when compared with controls (P<0.001). The association of hypoadiponectemia with visceral fat accumulation and MS is known (Jang-Young et al., 2013). Excess adiposity in obesity might be associated with down regulation of adiponectin secretion and with decreased expression of ADP receptors, which is likely to contribute to insulin resistance and dyslipidemia (Antoniades et al., 2009). The positive relationship of adiponectin with SHBG and vice versa in the cases only is not clear but may together with oestrogen play a role in cardioprotective mechanisms in women with MS.

Conclusion

Alterations in the levels of leptin and adiponectin in the cases may relate to increased adiposity and roles in cardioprotective mechanisms. All reproductive factors except FSH were similar in both cases and control in this study. The increased FSH levels in the cases than control may be associated with their increased age and also compensatory to maintain adequate oestrogen levels. These findings suggest that reproductive function is sustained in premenopausal women with MS with the likelihood of having children.

Abbreviations: **17β-HSD,** 17β Hydroxysteroid dehydrogenase; **AM,** age at menarche; **BMI,** body mass index; **BP,** blood pressure; **CVD,** cardiovascular disease; **DBP,** diastolic blood pressure; **DOP,** duration of menstrual period; **ELISA,** enzyme linked immunosorbent assay; **ETR,** oestrogen testosterone ratio; **FAI,** free androgen index; **FPG,** fasting plasma glucose; **FSH,** follicle stimulating hormone; **HDLC,** high density lipoprotein cholesterol; **K3 EDTA,** ethylene diamine tetraacetic acid; **LH,** luteinising hormone; **LOMC,** length of menstrual cycle; **MS,** metabolic syndrome; **NA,** number of children alive; **NLP,** number of live births; **NOP,** number of pregnancies; **NPCT,** number of pregnancies carried to term; **P,** probability; **SBP,** systolic blood pressure; **SHBG,** sex hormone binding globulin; **T2DM,** type 2 diabetes mellitus; **WC,** waist circumference.

Conflict of Interests

The authors have not declared any conflict of interests.

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