

Association between Serum Leptin and Anti-Mullerian Hormones in Women with Infertility in Ogbomoso Southwest Nigeria

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Abstracts: Background: One in every five women in Nigeria suffers infertility, 81.0% of whom occurs as a result of an underlying factor. However, available data on evaluation of ovarian function as an index of fertility are largely cycle-dependent and their usefulness confounded by the use of contraceptives. This study assessed more reproducible markers of ovarian function and determines the association between serum Leptin and Anti-mullerian Hormones in Ogbomoso municipal, Southwest Nigeria. Methods: The study was age-matched case-control in a 1:1 ratio involving 64 fertile women who met the inclusion criteria. It was conducted between January and May 2016 at LadokeAkintola University Teaching Hospital (LTH)Ogbomoso. The LTH Research Ethics Review Committee granted ethical approval for the study besides informed consent from the study participants. Serum leptin and AMH levels were measured by Enzyme Linked Immunosorbent Assay (ELISA) method. Appropriate statistical test was used to analyse encrypted data using IBM Corp Statistical Package for Social Sciences (SPSS) TM for Windows version 23.0 (Armonk, NY: IBM Corp). The confidence level was set at 95% and $p < 0.05$ level was significant. Results: One hundred and twenty-eight women with a mean age 32.9 (5.8) years (standard deviation) were recruited for the study. The median (interquartile range) of anti mullerian hormone (AMH) and leptin of the infertile women were 3.6(1.6-11.9) and 300.5(163.8-816.9) respectively. The statistically significantly higher median (IQR) of AMH (10.68 versus 1.7ng/ml; $p < 0.0001$) and leptin (657.64 versus 175.26 ng/ml; $p < 0.0001$) were observed between the fertile and the infertility arm. A weaker positive correlation coefficient was observed between Leptin and AMH level in infertile women ($R=0.445$, $p < 0.001$) compared with the fertile arm ($R=0.765$, $p < 0.001$). There were no significant association between Leptin, AMH with body mass index and age of the respondents. Conclusion: A higher median and stronger correlation coefficient of serum leptin and AMH was associated in fertile women compared with infertile women in Ogbomoso municipal. There were no significant association between Leptin, AMH with body mass index and age of the respondents.

Keywords: Leptin, AMH, infertility, Body mass index, Obesity

1. Introduction

Infertility is the inability of a sexually active couple to conceive in spite of adequate unprotected coital exposure over a minimum of one year period [1]. One in every five women in Nigeria suffers infertility, 81.0% of whom occurs as a result of an underlying factor while 22.7% are due to idiopathic causes [2]. As a consequence of the high premium culturally placed on fertility, women of childbearing age suffer untold psychosocial problems consequent to infertility [3]. Among the top reasons for gynaecological consultation in Nigeria, infertility has been reported as the most frequent reason for hospital visits[4], [5].

In the past two decades, there has been a substantial improvement in knowledge, interventional measures and technology for assisted reproductive techniques (ART) [6]. The services for the management of infertility has also become more readily available in most of the country hence

the need for proper evaluation and monitoring of ovarian reserve and response in women of childbearing age [7], [8].

Traditionally, ovarian function as an index of fertility is usually evaluated via assay for LH, FSH and estrogen level. However, these hormones are cycle-dependent and their stability is affected by the use of oral contraceptive drugs. [9], [10]. The reproducibility of AMH between consecutive cycles in the same woman, in distinction from FSH, estradiol and inhibin B, permits clinicians to have a reliable serum marker in prediction of ovarian response in assisted reproduction cycles [11]. In the same vein, Leptin has major physiological effects on puberty, menstrual cycle, pregnancy, lactation and early embryo development [12].

In spite of the high prevalence of infertility and a superior ovarian function profile using Leptin and AMH, the use of these hormones in evaluating ovarian function is limited in Nigeria. No reference data for the hormones levels among

women of childbearing age in Ogbomoso community, in spite of the availability of two tertiary health centres capable of offering assisted reproductive techniques to the community.

Leptin is the hormone product of the LEP gene and was originally thought to be produced only by the adipocytes to modulate satiety and energy homeostasis [13], [14]. Studies have shown that leptin is also produced by human ovarian follicles - both in granulosa and cumulus cells. It was confirmed at mRNA and protein levels that human pre-ovulatory follicles expressed the leptin gene [15]. Granulosa cells (GCs) in the ovaries have receptors for both adiponectin and leptin [16], [17]. Leptin deficiency or resistance have been associated with obesity, diabetes and infertility in humans [18], [19]. Various literatures have reported a link of increase in adipokines production and direct inhibition of ovarian function [7]. Besides, circulating leptin levels positively correlate well with menstrual cycles. Leptin does not only modify gonadotropin-releasing hormone and gonadotropins production, but it also plays an important role in the functioning of the ovary and endometrium and takes part in the development of an embryo [21].

Furthermore, anti-mullerian hormone, a dimeric glycoprotein and member of the transforming growth factor-beta family, is produced by granulosa cells in preantral and early antral follicles within the ovaries and is correlated with ovarian reserve [22]. AMH inhibits recruitment of primordial follicles and its concentration is proportional to the number of ovarian follicles that are developing [23], [24]. AMH is one of the most reliable markers for ovarian reserve and is commonly used in assisted reproduction as a predictor of ovarian response to controlled ovarian hyperstimulation (COH) for IVF [25]. It is associated with the number of oocytes retrieved in an IVF cycle [26]. AMH is also used to counsel patients who are interested in future reproduction and desired information on their reproductive lifespan as it can be used to predict the timing of menopause [24]. There is a well-established relationship between age and AMH, with levels declining as women grow older.

Study have shown that obese women with elevated serum and follicular fluid (FF) leptin levels have suppressed serum and follicular fluid adiponectin [16] levels, likewise human recombinant leptin down-regulates AMH and AMH receptor (AMHR-II) in infertile women [27]. This study therefore sorts to determine the association between serum leptin and AMH in women with infertility in Ogbomoso land.

2. Subjects and Methods

This study was conducted at Ladok Akintola University of Technology Teaching Hospital (LTH) Ogbomoso, Southwest Nigeria. The LTH Research Ethics Review Committee granted ethical approval for the study. In addition, we obtained consent from the study participants. The study design was age-matched case-control study conducted between January and May 2016 involving 64 subjects with 64 controls.

Consecutive patients with infertility were recruited at the Obstetrics and Gynaecology fertility clinic. Age-matched

controls consisting of apparently healthy women of childbearing aged were selected from the outpatient clinic of the department. The inclusion criteria were age between 18 and 45 years (reproductive age group), regular menstrual cycle length of 21 to 35 days, women who consented to the study and history of infertility. Women with a previous history of myomectomy, oophorectomy, hysterectomy, or any disease affecting the ovaries, biochemical or radiological findings suggestive of poly-cystic ovarian syndrome, diabetes mellitus, and thyroid disease and those on hormone therapy or any drug that interferes with menstrual cycle were excluded from the study.

Five millilitres of venous blood was collected aseptically on day 3 of the menstrual cycle into well labelled serum separator gel bottles for measurement of serum leptin and anti-mullerian hormones from eligible women. The samples were separated by centrifugation at 2000 - 3000g for 20 minutes and sera obtained into labelled plain bottles, stored at -20°C for onward analysis.

2.1 Sample processing

The samples were processed in duplicates at the Metabolic Research Laboratory of Department of Chemical pathology Ladok Akintola University of Technology Teaching Hospital, Ogbomoso. Control sera and calibrator were included in each batch. Serum leptin was quantified with human leptin and Serum AMH was quantified with human AMH Enzyme Linked Immunosorbent Assay (ELISA) kit manufactured by Span Biotech Ltd., Hong Kong using a double-antibody sandwich ELISA according to the manufacturer's manual. The sensitivity of the assay was 0.01 ng/ml. After incubation, the absorbance was read at 450 nm within 30 minutes using micro-plate ELISA reader (LT 4000).

2.2 Statistical analysis

Data collected in a study proforma were entered into a Microsoft access file and analysed using IBM Corp Statistical Package for Social Sciences (SPSS) TM for Windows version 23.0 (Armonk, NY: IBM Corp). Frequencies and proportions were computed for categorical variables. Measures of central tendency (mean, median and mode) and dispersion (standard deviation, variance) of quantitative variables were determined. Student t-test was used to compare means of normally distributed continuous variables while Mann-Whitney-U test and Kruskal-Wallis test was used to compare median values of non-parametric variables of leptin and AMH. Differences between proportions of categorical variables were evaluated using the Chi-square test. The Spearman's correlating technique was used to estimate the correlation between leptin and AMH. Results were presented in tables and figures. The confidence level was set at 95% and $p < 0.05$ level was significant.

3. Results

Of the 142 recruited for the study only 128 participants had sufficient data giving a response rate of 98.6%. The mean (standard deviation) age of the study population is 32.9 (5.8).

No significant difference between the age of the subjects and control (F=0.065 p=0.443)

1.1 Table 1 shows the social demographic characteristics of the study participant. Eighty-four (65.7%) of the participant were aged 28-37 years old. Half of the participants (51.6%) had a university level of education and are largely in the infertile sub-population 34(54.6 %). The predominant occupation of the participant 61(47.7%) were civil servants.

Table 1: Sociodemographic characteristic of study participants

Variables	Characteristics	Frequency	Percentage
Age	18-22	4	3.1
	23-27	12	9.4
	28-32	44	34.4
	33-37	40	31.3
	38-42	18	14.1
	43-45	10	7.8
Marital status	Married	127	99.2
	Single	1	0.8
Religion	Islam	34	26.6
	Christianity	94	73.4
Educational Status	Primary	10	7.8
	Secondary	15	11.7
	Post-Secondary	30	23.4

Occupation	University Graduate	66	51.6
	Others	7	5.5
	Trader	27	21.1
	Civil Servant	61	47.7
	Full House Wife	7	5.5
	Student	11	8.6
Ethnicity	Others	22	17.2
	Yoruba	125	97.7
	Ibo	1	0.8
Marital age in years	Hausa	2	1.6
	0-4	52	40.6
	5-9	53	41.4
	≥10	23	18.0

1.2 Table 2 Comparison of anti mullerian hormones and serum leptin between infertile and fertile women. The median (interquartile range) of anti mullerian hormone (AMH) and leptin of the infertile women were 3.6(1.6-11.9) and 300.5(163.8-816.9) respectively. The median (IQR) of AMH (10.68 versus 1.7ng/ml; p=< 0.0001) and leptin (657.64 versus 175.26 ng/ml; p=< 0.0001) in the fertile women were statistically significantly higher than those with infertility. Infertile subjects have significantly lower median AMH 8.43 (95% CI 6.02 to 10.84) and lower median Leptin 523.01 (95% CI 366.60 to 678.42)

Table 2: Comparison of measured level of AMH and Leptin between fertile and infertile women

Biomarker	Status	Median	Lower quartile	Upper quartile	Min max	Average rank	U-test	P-value
AMH (ng/ml)	Fertile	10.68	5.13	15.44	1.50 21.10	38.79	402.50	< 0.0001
	Infertile	1.71	0.59	15.44	1.50 21.10	90.21		
Leptin (ng/ml)	Fertile	657.64	241.29	1150.22	99.70 1745.30	80.07	1051.50	< 0.0001
	Infertility	175.26	156.31	322.12	50.00 1540.40	48.93		

(AMH Infertile 95% CI 0.94-2.10; fertile 95% CI 6.24-14.04) 95% CI 4.95-10.91 overall

Leptin Infertile 95% CI 164.62-199.10; fertile 95% CI 390.68-824.40) 95% CI 150.75-539.62

Figures 1 and 2.Correlation between Leptin and AMH

A weak but statistically significant positive correlation coefficient (R=0. 445; p<0.001) exists between Leptin and AMH in infertile women compared to a stronger coefficient (R=0. 765; p<0.001) noted in the fertile arm as shown in figures 1 and 2.

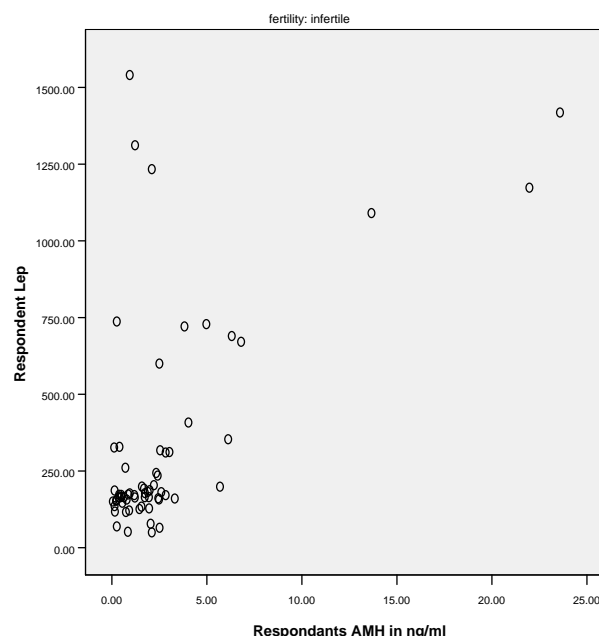


Figure 1: Correlation between serum leptin and anti mullerian hormone among the infertile population

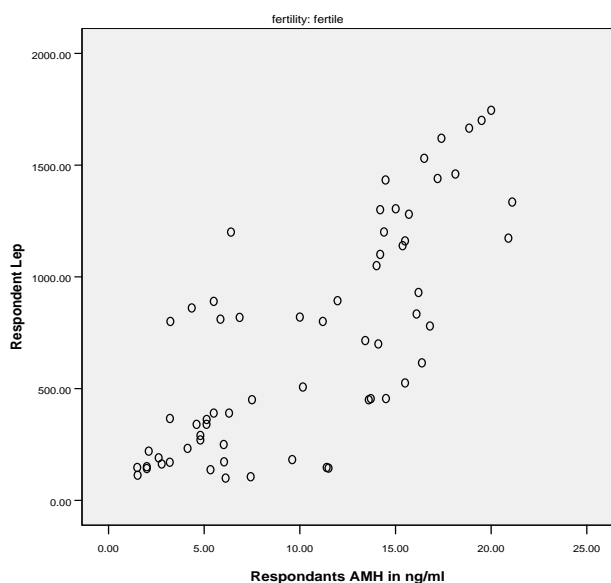


Figure 2: Correlation between serum leptin and anti mullerian hormone among the fertile population

1.3 Table 3 Association between biomarkers and the variables of body mass index and age group and marital age. There were no significant association between AMH, body mass index and age of the respondents in the general study population. Women aged 23-32 years had significantly higher levels of leptin compared with ages 18-22 and those older than 32 years. A sub-analysis of the fertile population however quantile regression adjusting for age, BMI and years of marriage. Adjusted median AMH 8.88 (95% CI 6.29 to 11.47). Quantile regression adjusting for age, BMI and years of marriage. Adjusted median Leptin 499.90 (95% CI 333.67 to 666.12)

Table 3 (a): Association between biomarkers and the variables of BMI and age group

AMH (ng/ml)	BMI category (n)	Median	Lower quartile	Upper quartile	Min max	Average rank	K-test	P-value
BMI	< 18.5 (4)	2.22	1.08	5.04	0.94 6.85	50.63	2.0587	0.5603
	18.5-24.9 (36)	5.42	1.83	14.79	0.26 23.58	71.06		
	25.0-29.9 (47)	3.20	1.67	13.06	0.14 21.97	63.65		
	>30.0 (41)	3.31	1.36	8.03	0.05 18.85	61.07		
Age	18-22(4)	6.73	1.825	13.85	1.69 16.2	71.00	4.3334	0.5025
	23-27(12)	4.31	1.375	8.9	0.35 14.2	60.75		
	28-32(44)	4.475	1.2	14.755	0.12 23.58	67.11		
	33-37(40)	5.225	1.66	14.3	0.14 21.97	68.47		
	38-42(18)	2.93	2	9.6	0.05 14.1	62.25		
	43-45(10)	2.05	1.52	2.54	1.21 3.31	43.05		

Table 3 (b): Association between biomarkers and the variables of BMI and age group

Leptin (ng/ml)	BMI category (n)	Median	Lower quartile	Upper quartile	Min max	Average rank	K-test	P-value
BMI	< 18.5	809.69	482.06	1179.64	163.65 1540.40	86.75	2.1767	0.536
	18.5-24.9	353.12	164.62	910.30	50.00 1745.30	67.99		
	25.0-29.9	250.00	163.12	885.40	52.07 1460.20	62.80		
	>30.0	243.56	163.54	683.60	69.33 1665.52	61.22		
Age intervals	18-22(4)	168.465	136.195	561.415	128.04 930.25	46.75	16.2611	0.006
	23-27(12)	275.57	155.4	718.235	78.04 1300.6	61.58		
	28-32(44)	452.69	176.285	875.635	52.07 1700.06	72.95		
	33-37(40)	359.825	172.315	1156.415	65.00 1745.3	72.10		

	38-42(18)	186.425	162.91	507.08	105.89 893.56	53.00		
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4. Discussion

The finding of the majority of the study participants in the infertile arm within the age group of 28-37 years with predominant University education are in keeping with the report by Lutchman et al [28], who showed that postponement of conception due to career pursuit led to delayed conception as a result of decline female fertility.

Recent report has shown that the age at marriage has significantly increased in the past 2 decades globally with the implication that the incidence of infertility may be on the rise thus a need for a more reproducible and reliable marker are needed for proper monitoring of reduced ovarian reserve and response such as leptin and AMH [29] - [31]. This study findings, showed a lower median (IQR) of leptin and AMH in the infertile women compared with the fertile population, but high serum leptin was observed by other researchers [32], [33]. In contrast, Wertel *et al* observed no such changes in serum leptin levels in their study population [34]. While, in some others, the increase in serum leptin levels was noticed in both fertile and infertile groups and high serum leptin levels in these patients was not contributing factor of infertility [35]. However, Serum AMH outcome was similar to the findings of Kalaiselvi et al [36]. Reduction in the value of AMH in the infertile could be due to early reduction in the number of primordial follicles left in the ovaries [37], thus, leading to reduction in ovarian reserve in the infertile women. The difference in findings could be due to a number of factors including genetic makeup, sample sizes, age range and body mass index, BMI.

There is a statistically significant and positive correlation between Leptin and AMH level in infertile women while the correlation among fertile women is stronger and also statistically significant. The association between adiponectin and leptin and AMH has been analysed in several studies, but conflicting results have been reported. Olszanecka-Glinianowicz and colleagues as well as Park et al reported a significant relationship between adiponectin and AMH, but that leptin was not significantly correlated with AMH in women with and without PCOS [38], [39]. Shen et al found no association between adiponectin and AMH in women with and without PCOS [40]. Also in an experimental study done by Merhi and colleagues, who reported that AMH decreased when granulosa cells were treated with leptin, but that adiponectin treatment did not affect AMH expression [27]. Another finding of an inverse association between leptin and AMH in a cohort of women with only a small prevalence of PCOS concurs with the findings of Merhi and colleagues in Bernardi et al [41]. More studies are needed on the correlation between leptin and AMH among infertile women with greater sample size, taking the BMI level into consideration. This study therefore, shows no significant association between AMH, body mass index and age of the respondents.

Previous studies into the relationship between obesity and AMH have yielded mixed results. Dölleman et al reported that BMI was not significantly associated with age-specific

AMH percentiles in women with a mean BMI of 24.3 kg/m² [42]. Similarly, neither Sahmay and colleagues nor Halawaty et al found differences in AMH concentrations between women with and without obesity [43], [44]. In a study of 36 women with a mean age of 45, Su et al reported that AMH concentrations were 77% lower in individuals with obesity compared to those of normal weight [45]. Freeman and colleagues examined 122 women with a mean age of nearly 46 and reported that women with obesity had AMH concentrations that were 65% lower than women without obesity [46]. Steiner et al examined 20 women with a mean age of 29 who were taking oral contraception and reported that AMH concentrations were 34% lower in women with obesity compared to normal weight women [47]. Bleil and colleagues reported that AMH decreased by 1.5% with each one unit increase in BMI in a cohort of 947 women with a mean age of 35 [48]. Moy et al described a negative correlation between BMI and AMH in 159 Caucasian women but not in 99 African American Women [49]. Buyuk et al found an inverse association between BMI and AMH in 152 women with decreased ovarian reserve, but not in 138 women with normal ovarian reserve [50].

The inconsistencies in the literature may be because prior studies did not have sufficient numbers of women in very high BMI groups to capture an association with AMH. Women aged 23-32 years had significantly higher levels of leptin compared with ages 18-22 and >32 years. No associated serum leptin level, body mass index and age of the respondents. The serum level of leptin was highest in BMI 18.5 – 24.9 (N=36 with infertile 16) followed by BMI >30 (N= 41 with infertile 24), this account for 62.5% of infertile women with high level of leptin. However, in a study of the BMI groups <20 and between 20 and 24.9 (low to normal), significantly have higher levels of leptin in the infertile women [34]. It is noteworthy that Leptin plays an important role in follicular development and consequent luteal function [51]. Furthermore 71.9% of infertile women in our study fall under overweight and obesity, this may account for infertility in them. Women who have a higher BMI have decreased responses to fertility medications [52], fewer oocytes retrieved [53], and lower pregnancy and live birth rates [54] than those who have a normal BMI. Also, it has been suggested that obesity impairs ovarian function [55]. Grodstein et al. [56] also revealed that anovulatory infertility was higher in overweight and obese patients whose BMI was found to be greater than 26.9 kg/m². Although other causes of infertility have to be looked into in the infertile group because 65.7% of fertile women also fall under overweight and obesity in our study.

5. Conclusion

The present study shows that the median of Leptin and AMH were statistically significantly higher among fertile women than infertile women. Also, there is positive correlation between Leptin and AMH among fertile and infertile women and statistically significant. But the correlation is stronger in fertile women. Other causes of

infertility have to be looked into within the infertile group for better management.

6. Acknowledgments

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7. Conflict of Interest

Authors declared no conflict of interest.

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