ejpmr, 2017,4(06), 138-142

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

RELEVANCE OF SERUM LH/FSH/PROLACTIN AND ANTI MULLERIAN HORMONE ESTIMATION IN INVITRO FERTILIZATION

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Article Received on 14/04/2017 **Article Revised on 05/05/2017** **Article Accepted on 26/05/2017**

ABSTRACT

Background: Infertility has been considered a field of importance in public health circles due to its high prevalence and its social effects on affected couples and families. Detection and evaluation of incidence of infertility and prevalence in a population is achieved through surveillance which includes determination of the different types of infertility clinically and the use of various laboratory investigations for its detection and treatment. **Aim:** This study aimed at evaluating the relevance of serum AMH, LH, FSH and Prolactin measurement in women seeking invitro fertilization in our environment. **Methodology:** This was a cross sectional prospective study were women assessing invitro fertilization (IVF) intervention at Kauna Specialist Hospital, Jos, Nigeria were enrolled. Demographic data was collected using self administered questionnaires with special attention focused on known history of female infertility. 10 mls of venous blood was collected from each subject, into plain containers and allowed to clot. The samples were analyzed for hormone concerntrations using enzyme immunoassay (EIA), according to the World Health Organization (WHO) matched reagent programme protocol (manual) for EIA kits (protocol/version of December 1998 for Prolactin, LH, FSH; and protocol 09.3.1 for AMH).Data generated were analysed using SPSS version 21 for simple statistical analysis and comparism of means between groups, $p<0.05$ was considered significant. **Results:** A total of 124 infertile women seeking invitro fertilization due to different etiology of infertility were monitored in the course of their treatment. The positive pregnant women had a mean serum AMH of 11.61ng/ml,SD=13.896 while the non pregnant women had mean =27.5ng/ml5, SD=43.919, p=0.003) A pearson correlation(r=-0.201,p=0.025) was obtained for pregnancy outcome following IVF and serum AMH level. In addition, r=0.705(p=0.000) was obtained when serum FSH and LH were compared for possible association based on IVF success. **Conclusion:** Our study suggests that serum AMH levels decreased steadily with increasing age in cases of infertility. In addition, Serum FSH and LH had a positive correlation which may imply that they are good predictors of ovarian reserve.Mesurement of serum AMH, LH, FSH and Prolactin are relevant for evaluation of possible IVF success rate.

KEYWORDS: IVF, AMH, Female infertility.

INTRODUCTION

According to the World Health organization (WHO), infertility can be defined as a condition in which a couple of child bearing age is unable to conceive within 12 months or longer of unprotected sexual intercourse (Araoye, 2003, AlHadi.2016). Infertility has been considered a field of importance in public health circles due to its high prevalence and its social effects on affected couples and families.

Infertility in developing countries like Nigeria has always been a neglected reproductive health concern, despite the fact that it has devastating consequences for the women involved. The neglect of infertility in formal health care is often explained in terms of population control (decreasing fertility growth is considered to be more important than treating infertility); the heavy burden of life-threatening conditions like HIV/AIDS and maternal mortality; and the scarcity of health resources in these countries (Okanofua, 1996; Ombelet, 2009; Van Balen and Gerrits, 2001).

Some of the key indicators commonly monitored in cases of suspected infertility include semen quality, time-to-pregnancy, recurrent pregnancy loss and different laboratory tests. (CDC, 2014) In addition, public health

also plays an important role in detection of infertility by collection of population based data aimed at identifying key indicators related to screening, diagnosis, laboratory services, specific infertility treatment mandates which may influence counseling and treatment options (Broekmans,2006).

Currently, infertility is managed through counseling, treatment of the cause of infertility and use of newer technologies such as artificial reproductive fertilization (ART) which may include Invitro Fertilization (IVF) and Intra Uterine Insemination.

In the United States, the number of IVF cycles increased from 99,629 in 2000 to 163,039 in 2011.The use of invitro fertilization (IVF) option in Nigeria is currently on the increase although CDC has reported that it could pose health risks for women, men and children. This is due to the use of drugs for manipulating ovulation in such couples, these drugs may lead to ovarian hyperstimulation syndrome (OHSS) characterized by enlargement of the ovaries which is a life threatening condition. (CDC, 2014).

The IVF intervention is an expensive technology and in the United States, there are disparities in the use and access of this service. According to the Health Day News, 2014, Black women undergoing invitro fertilization (IVF) are only about half as likely as white women to become pregnant. In addition there is also paucity of data on serum fertility hormones and their relevance in the management of infertility using IVF. Estimation of serum AMH and other fertility hormones before IVF intervention are currently done mainly in the developed countries like US and England with little been done in Nigeria (CDC,2005). Since IVF is an expensive procedure, it would be ideal to evaluate and counsel couples on the implications of this procedure based on fertility hormone levels before consenting to the IVF procedure. This work therefore sought to evaluate/determine the relevance of serum AMH, LH, FSH and Prolactin measurement in women seeking invitro fertilization.

MATERIALS AND METHOD

This was a cross sectional prospective study were women assessing infertility services (IVF) at Kauna Specialist Hospital in Jos metropolis were recruited. The study participants were women who were confirmed infertile based on different diagnostic tests carried out on the patients.

Jos the Plateau State capital is situated almost at the geographical centre of Nigeria and about 179 kilometres (111 miles) from Abuja the nation's capital city, Jos is linked by road, rail and air to the rest of the country. The city is served by Yakubu Gowon Airport, but its rail connections no longer operate as the only currently operational section of Nigeria's rail network is the western line from Lagos to Kano. At an altitude of 1,217 m (3,993 ft) above sea level, Jos enjoys a more temperate climate than much of the rest of Nigeria. Average monthly temperatures range from 21–25 °C (70–77 °F), and from mid-November to late January, night-time temperatures drop as low as 11 °C (52 °F). Hail sometimes falls during the rainy season because of the cooler temperatures at high altitudes (Wikipedia,2016) Demographic data was collected using self administered questionnaires with special attention focused on known history of female infertility in patients. In addition, the age, years of infertility and occupation of the participants were also sought and obtained from the consenting participants.

Statistical analysis was performed using SPSS ver. 12.0 (SPSS, Chicago, IL, USA). To determine the correlation between AMH and other variables, the data was analyzed by Pearson's correlation. Simple statistics and ANOVA was performed to present the age-related changes in AMH, FSH., LH and Prolactin. Each variable was presented as mean±SD with $p<0.05$ considered statistically significant.

RESULTS

Demographic Characteristics of Participants

A total of one hundred and twenty four (124) infertile women seeking invitro fertilization due to different etiology of infertility were enrolled for this study in Plateau state. These women were considered infertile due to their inability to conceive despite unprotected sex for two years. Out of the 124 women enrolled, 53(42.7%) were reported infertile due to tubal related factors while only 1(0.8 was considered infertility due to ovarian cyst. The age distribution showed that participants within age group, 21-25years had 1(0.8% participant)while age groups 26-30years,31-35years,36-40years,41-45years ,46-50years and 51-55years had 15(12.1%),27(21.8%),28(22.6%),39(31.5%),12(9.7%) and 2(1.6%) participants respectively. Of the women seeking fertility through IVF, 106(85.5%) have no biological children while 14(11.3%) had one biological child,3(2.4%) had 2 biological children and 1(0.4%) had four biological children. In addition, years of infertility varied with 38(30.6%) been reported as been infertile for between 2-6years,46(37.1%)between 7-11years ,25(20.2%) for between 12-16years and 15(12.1%) reported as being infertile for more than 17years as shown in table 1.

Table 1: Demographic Characteristics of Participants.

Characteristics	Number (%)
Age group(yrs)	
21-25	1(0.8)
26-30	15(12.1)
31-35	27(21.8)
36-40	28(22.6)
41-45	39(31.6
46-50	12(9.7)
51-55	2(1.6)
Any biological children?	
None	106(85.5)
1 child	14(11.3)
4 children	1(0.4)
Years of infertility(yrs)	
2-6	38(30.6)
7-11	46(37.1)
12-16	25(20.2)
>17	15(12.1)
Occupation	
Buissness	30(24)
Civil servant	72(58.1)
Students	7(5.6)
Applicants	7(5.6)
Housewife	7(5.6)
Missionary	1(0.8)

Relationship between years of infertility and serum level of Hormones (FSH, LH, PROLACTIN and AMH) among the infertile women

A one-way between groups analysis of variance was conducted to explore the impact years of infertility on serum levels of fertility hormones. The participants were divided into four groups according to their years of infertility ie 2-6years,7-11years,12-16years and greater than 17years.There was no statistical significant difference at $p<0.05$ for serum AMH($F(3,120)=1.10,p=0.35$),FSH($F(3,115)=0.716,p=.544$),LH($F(3,115)=.826,p=.482$) and PROLACTIN ($F(3,117)=.386,p=.763$) based on the years of infertility.

An independent-samples t-test was conducted to compare the serum AMH, FSH, Prolactin and LH for the negative and positive pregnant women with basic statistics shown .There was a significant difference in the serum AMH levels for PT negative women(M=27.55ng/ml,SD=43.92)and the PT positive women (M=11.61ng/ml,SD=13.89,$t(122)=2,264,p=0.025$. The magnitude of the difference in means (mean difference=15.94,95%CI:26.416-29.873)was quite large.

Table 2: Shows the relationship between years of infertility and hormone level.

ANOVA						
		Sum of Squares	**Df**	**Mean Square**	**F**	**Sig.**
Antimullerian Hormone	Between Groups	4633.610	3	1544.537	1.102	.351
	Within Groups	168226.969	120	1401.891		
	Total	172860.579	123			
Follicle Stimulating Hormone	Between Groups	823.590	3	274.530	.716	.544
	Within Groups	44076.102	115	383.270		
	Total	44899.692	118			
Luteinizing Hormone	Between Groups	346.224	3	115.408	.826	.482
	Within Groups	16066.164	115	139.706		
	Total	16412.388	118			
Prolactin	Between Groups	999.289	3	333.096	.386	.763
	Within Groups	100846.468	117	861.936		
	Total	101845.757	120			

Pattern of serum AMH among infertile women

The mean serum AMH concerntration for the participating women was 22.28ng/ml,SD=37.9 with a minimum of and 0 maximum of 201. The women who had been infertile for between 2-6years had AMH mean±SD concerntration of 25.35±41.23ng/ml, women with a history of infertility between 7-10 years had AMH concerntration of 27.05±43.52ng/ml while the serum AMH concerntration for women with a history of infertility for 12-16years had mean serumAMH of 16.32±26.32ng/ml greater than 17 years infertility group recorded mean serum AMH of 9.80±15.685ng/ml. When an independent-samples t-test was conducted to compare the serum AMH level for the IVF successful pregnant women and the pregnancy negative women there was a significant difference between these groups. The positive pregnant women had a mean serum AMH of 11.61ng/ml,SD=13.896 while the non pregnant women had mean =27.5ng/ml,SD=43.919;$t(109.3)=3.015,p=0.003$,two-tailed) The magnitude of the mean difference was 15.939ng/ml which is large.

Table 3: Showing relationship between serum AMH level of successful and unsuccessful IVF.

Results for independent -samples t-test										
		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
antimullerian Hormone	Equal variances assumed	16.104	.000	2.264	122	.025	15.939	7.039	2.005	29.873
	Equal variances not assumed			3.015	109.393	.003	15.939	5.287	5.461	26.416

DISCUSSION

In our study which sought to understand the relevance of measuring serum hormone concerntration (LH, FSH, PROLACTIN and AMH) in infertile women seeking IVF, a total of 124 willing participants enrolled for the study. The findings of this work suggests that majority of women seeking IVF are within the age group of 41-45 years while least group that sought IVF intervention were between age group 17-21years. Sule et al(2008), in his work reported that the age at high risk of infertility is age group between 36-45 while age group with the least rate of infertility was considered to be 15-25years.Findings are also in agreement with Olugbenga et al(2014) who reported a low awareness of IVF in his study with a high level willingness to accept IVF intervention by civil servants .He also reported that the high cost of IVF in the south western Nigeria was responsible for rejection of this option for infertility intervention. Worthy of note is the high incidence 53(42.7%) of tubal related issues as the cause of infertility among the subjects in this work followed by infertility associated with ovarian cyst 1(0.8%).Previous work done by Sule et al(2008) in western Nigeria reported tubal factor, uterine factor, and ovarian factor were the major cause of infertility in this environment . The success rate for pregnancy in this study was shown as 16.1% which implies live birth of babies is different from the report of around 25% success rate as reported by Giwa-Osagie(2002).This success rate also implies a failure rate of about 84%,which is distressing for those who went through the financial and heavy psychological cost of the procedure.

Serum FSH and LH in this study had a positive correlation which may imply that they are good predictors of ovarian reserve. This finding is supported by the work of fertility researchers who have in addition suggested the use of FSH/LH ratio for determination of IVF cancellation. Recently, there was a report that elevated day 3 FSH/LH ratio ≥2 is associated with higher rates of cancellation in InVitro Fertilization (IVF)-embryo transfer cycles (Liu et al,2008) and some studies have shown that the day 3 FSH to LH or LH to FSH ratio can be used as a predictor of the ovarian reserve (Liu, et al(2008).

This work shows that the mean serum AMH level for pregnancy to occur is 11.61ng/ml whereas women with mean serum AMH of 27.55ng/ml were unable to conceive. Various research has shown that AMH is an important predictor of ovarian reserve and this helps in determining the chances that a woman will get pregnant(Bhide,2013). Bhide et al(2013) in a retrospective study carried out at a university IVF centre in which he included 820 women who underwent IVF treatment in 1 year showed that there was a strong positive correlation seen between AMH and the number of eggs obtained during IVF treatment. In his study, he reported a significant difference in pregnancy rates (24.4% and 40%) between the lowest and highest quartiles of AMH. Our study is in line with this work as the AMH value for the enrolled women ranged from 0ng/ml to 201ng/ml with highest pregnancy rate at the lower percentile of AMH level. This implies that the age of infertility does not influenced the AMH level however, the age of the of the infertility may have an impact on the AMH level. An independent-samples t-test conducted revealed that AMH level for the IVF successful pregnant women and the unsuccessful cases was significant. In the work of Seifer et al.(2011) in which he examined age-specific serum AMH values for 17,120 women of reproductive age from 24 to 50 years old presenting to fertility centers within the United States. In his work, serum AMH levels decreased steadily with increasing age. However, the results of that study derived from the serum AMH levels of women during fertility evaluation, and thus were not representative of the general population.

CONCLUSION

In conclusion,serum levels of AMH, LH, FSH and Prolactin are relevant for evaluation of possible IVF success and this should be considered before registering women for possible IVF. This will help in counseling of patients prior to IVF and may serve for alleviating any

financial berden associated with IVF procedures. Especially in women seeking invitro fertilization.

This work has also shown that infertile women in Jos are able to conceive with a mean serum AMH of about 11ng/ml. With this finding it might be worth while to determine the normal range of AMH in our environment. The possible success rate of IVF in infertile women based on some serum AMH, LH, FSH and Prolactin level has shown that there is a positive correlation between FSH and LH, in addition to a weak relationship between AMH and pregnancy outcome. More work will need to be done on a larger population of women to ascertain these variations and relationship between these hormones. There was no relationship between serum hormone levels and years of infertility but a positive relationship existed between age and serum FSH. This calls for more work on the influence of age on FSH and possible remedy so as to improve the IVF success rate.

Overall, the application of these findings will be most relevant in the area of creating an opportunity for a health and educational talk regarding the role of serum LH/FSH/Prolactin and AMH estimation for assisted reproductive technique in the management of female infertility.

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