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ORIGINAL ARTICLE

Pituitary and gonadal hormone abnormalities amongst infertile women in the Southwest Region of Cameroon and related risk factors

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ABSTRACT

Background: Female infertility is partly due to reproductive hormone deregulation, involving the hypothalamic-pituitary-gonadal axis. A high prevalence of female infertility has been reported in the Southwest region of Cameroon, however, little attention has been paid to the hormonal contribution. **Objective**: This study reports on the implication of hormones in female infertility in two regional hospitals in the Southwest Region of Cameroon. **Methods**: A hospital-based case-control study was conducted in Buea and Limbe regional hospitals. Cases (n = 86), and controls (n = 40), comprising menstruating and breastfeeding mothers were enrolled from the infertility clinics and vaccination units respectively. A questionnaire was used to collect socio-demographic data and infertility risk factors. Serum follicle stimulating hormone (FSH), luteinizing hormone (LH) and oestradiol were measured on days 1–3 and progesterone on days 21–22 of the menstrual cycle, using ELISA method. Data were analysed using Mann Whitney *U*-rank, Chi-square tests and multiple logistic regression with $p < 0.05$ considered significant. **Results**: Most of the women (57 %) were aged between 26 and 35, and overweight or obese (77 %). Mann Whitney test showed a significant increase in FSH (12.47±5.57 IU/L) for cases than (8.88± 1.50 IU/L) controls ($p = 0.001$), a significant decrease in LH (6.55±7.19 IU/L) for cases than controls (9.57±2.75 IU/L), ($p = 0.001$), contrasted by a significant decrease in progesterone (13.48±5.89 ng/mL) for cases compared to controls (6.63±7.23 ng/mL), ($p = 0.001$). Oestradiol was not statistically significant ($p = 0.573$). Age of participant and age at menarche were the only statistically significant ($p = 0.001$), risk factors for infertility.

Conclusion: This study revealed that high follicle stimulating hormone and low progesterone are the primary hormonal abnormalities likely to be responsible for female fertility in the study area which were associated with increase in age and age at menarche.

Keywords: Female infertility, Risk factors, follicle stimulating hormone, luteinizing hormone, oestradiol, progesterone.

INTRODUCTION

Infertility, known as a couple's inability, to achieve pregnancy within 12 months of unprotected sexual intercourse [1], is a social threat that affects people from all communities worldwide, though the cause and magnitude vary depending on geographical location and socioeconomic status. Primary infertility occurs when a woman has never conceived, and secondary infertility occurs when she has had a previous pregnancy. About 30 % of infertility cases are primarily attributable to the

woman, 30 % to the man, 20 % to an interaction between the two and the remaining 20 % is unexplained) [2–5], though the woman is frequently blamed for the couple's infertility and subjected to psychological and social disrespect [5].

In Cameroon, childbearing defines a woman's identity and motherhood is of great social significance; as mentioned above, infertility has serious negative social effects [5–7]. It is estimated that 60-80 million couples worldwide suffer from infertility each year. Infertility has increased significantly in recent years with a global prevalence of 10-15 % [3], and is particularly high in South-East Asian and Sub-Saharan African countries. [4]. According to a systematic analysis published by the World Health Organization (WHO) in 2012, one in every four couples in developing countries suffers from infertility [2]. Infertility affects between 8 and 12% of reproductive-age couples worldwide [5]. Data on infertility in Cameroon is scarce due to very little research and policy focus. Previous data reports a national prevalence of 4.7% for primary infertility and 6.8% for secondary infertility [8] One of very few studies reported a prevalence of infertility of 19.2% in three hospitals in Douala, the economic capital of Cameroon [9]. The incidence of miscarriage rises with age, lifestyle changes, and defects in reproductive organs, which are highly vulnerable to oxidative toxicants and hormonal imbalance [6,7]. Hormonal imbalances are the leading cause of female infertility because they are essential for ovulation and the development of the corpus luteum, which prepares the uterus for implantation [6, 7, 10]. Women's hormones naturally fluctuate throughout their menstrual cycle and each woman's cycle is unique. The complex interplay of these hormone networks in the hypothalamic-pituitary-gonadal axis regulates secretion from other feedback system components. The effects of oestrogen dose and duration dependent, ensuring that a pre-ovulatory luteinizing hormone (LH) surge is induced only by a mature Graafian follicle under normal conditions. Progesterone appears to have little intrinsic action on gonadotrophin secretion but enhances negative feedback effects of oestradiol. It also has the important property of inhibiting the ability of oestrogen to induce positive feedback [6, 7, 10, 11]. Excess or deficiency of these hormones causes imbalance, which can result in irregular menstrual, ovulation disorders and low fertility or infertility.

Several studies on hormonal abnormalities associated with infertility [10] reported increased levels of anti-Müllerian hormone, LH, oestradiol, testosterone and decreased FSH levels in infertile women presenting with polycystic ovarian syndrome [10 -12]. A study in Nigeria found that reduced LH levels with consequent anovulation was the commonest presentation in infertile women [6]. Women of childbearing age in China presenting with oligomenorrhea were shown to have significantly increased levels of anti-Mullerian hormone, total testosterone, and androstenedione compared to women without with oligomenorrhea [11]. Meanwhile, Wali *et al*. found no link between thyroid dysfunction and the type of infertility (functional or mechanical), implying that hormones that do not play a primary role in conception may not contribute significantly to female infertility [12].

Previous retrospective investigations documented high prevalence (24%) of infertility amongst females visiting the gynaecological and maternity units of the Limbe and Buea Regional Hospitals in the South-West of Cameroon, with secondary infertility being the prominently diagnosed (17.6%) [4]. Although most of the affected couples were reported to suffer from preventable sexually transmitted infections (STIs), the contribution of hormonal imbalance was not assessed. Hence, the present study is designed to investigate female infertility in relation to reproductive hormone abnormalities in the Southwest Region of Cameroon.

METHODS

Study area and design

This was an analytical case-control study conducted at the Gynecology and Maternity units of the Buea and Limbe Regional hospitals in the Fako Division of the Southwest region of Cameroon. A questionnaire was designed and administered to the respondents. It was made up of subsections on demographic information; reproductive assessment, causes of infertility, assessment knowledge of infertility and the respondent's attitude towards infertility. The final section inquired on their treatment options and investigation of the studied reproductive hormones: FSH, LH progesterone and oestrogen.

Sample size and study participants

This study was approved by the Institutional Review Board of the Faculty of Health Sciences of the University of Buea (Reference number: 2019/1007-08/UB/SG/IRB/FHS) and authorization was obtained from the hospital administration. Each

participant signed the consent form after being thoroughly informed on the purpose and benefits of the study. The study enrolled 86 cases of confirmed infertile women. The women included as cases were in the reproductive age (15–49 years) and presented with failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse, at both health facilities. Women at menopause, and those whose male partners had been diagnosed with reduced infertility were excluded. The controls (40) were menstruating and breastfeeding mother less than 30 years attending the hospitals for infant vaccination. Women with amenorrhea, taking birth control pills, pregnant, having any medical issues that can hinder fertility were excluded from the controls.

Specimen collection and analysis

The menstrual cycle for each respondent was monitored to determine the stage of the monthly cycle suitable for sampling (follicular and luteal phase). A blood specimen was collected in two phases in the second or third day of the menstrual cycle for follicle stimulating hormone (FSH), luteinizing hormone (LH) and oestradiol and then one week after ovulation for progesterone. The blood (2 mL) was collected by venepuncture into a 4 mL red vacuum blood collection tube and the serum later separated by centrifugation at 3000 rpm for 30 minutes into a sterile Eppendorf tube. The serum was then frozen at -20 ºC. The hormones were measured by enzyme immunoassay using ERBAlisa 96 test kits (Calbiotech USA). The two gonadotropins LH and FSH were measured by sandwich ELISA while oestradiol and progesterone were measured by delayed competitive and competitive ELISA methods using streptavidin biotin technology at a wavelength of 450 nm with a microplate reader. Hormone levels were interpreted using the reference ranges provided in the ERBAlisa test kits.

STATISTICAL ANALYSIS

Data were analysed using Statistical Package of Social Science IBM-SPSS© version 20. Student t-test and Chi square test were used to compare mean ± standard deviation and frequencies for numerical and categorical variables. Comparisons between the cases and controls were performed using the parametric student-*t* test and non-parametric Mann-Whitney *U* rank test for continuous variables, while Chi-square test was used for categorical variables. Multiple logistic regression was used to further assess the contribution of hormones to infertility. In this analysis, all predictor variables were considered in the continuous scale. However, natural logarithm of hormonal variables was considered instead of raw values, given their distribution. Age was also included in this model, based on the preliminary finding in bivariate analysis. Statistical analyses with *p*-values < 0.05 were considered significant.

RESULTS

Socio-demographic characteristics of participants

Among the variables analysed with Chi square, there was a significant difference ($p = 0.0001$) in the age group between the cases and controls. The age group most affected by infertility among the cases was 26–30 years (37.2 %) compared to controls, 27 years (67.5 %). There was no difference in age at menarche between the cases and controls ($p < 0.978$). Among the cases, 20 (23.3 %) had normal weight and 66 were overweight (34.9%) or obese (41.9%). Although a change in the body mass index (BMI) affects reproductive hormones, the difference between the cases and control was not statistically significant ($p = 0.508$). There was no statistically significant difference concerning occupation.

Hormone levels in serum

High levels of FSH (12.47±5.57) were significantly ($p < 0.0001$) prevalent amongst the 86 (n=54, 62.8 %) infertile cases than the 40 controls (8.88±1.50) (n=6, 15 %). Low levels of progesterone were also significantly prevalent ($p < 0.0001$) among cases (13.48±5.89) (60.5 %) cases than controls (6.63±7.23). The distribution of luteinizing hormone levels amongst the two groups was not significantly different ($p = 0.135$), although higher and lower levels were likely to be found amongst infertile cases. Also, lower, and higher levels of oestradiol were frequently observed amongst the infertile cases (4.7% and 16.3% respectively) than the healthy controls (2.5% and 0% respectively) were statistically significant ($p = 0.019$). The distribution of hormonal levels is shown in Table 2.

Perceived causes of infertility among cases

The medians or distribution of the values of hormone levels for the cases and the controls were compared using Mann-Whitney U test to determine possible causes of infertility among the cases (Table 3). The levels of FSH, and progesterone were significantly higher ($p < 0.0001$ and $p < 0.0001$ respectively) in cases, while levels of LH were significantly lower ($p = 0.0001$) in the same group.

While including the age and all hormonal variables in multiple regression analysis (Table 4), it was observed that oestradiol was not associated with infertility status. For instance, increase in age had the odds of 1.2 to be related to infertile status (OR=1.225; 95%CI [1.100–1.468]; *p*=0.0018). An increase in a logarithmic unit of FSH results in a 34.7 times likelihood of being infertile (OR=34.715; 95%CI [4.759–451.164], *p*=0.0020), whereas an increase in a logarithmic unit of progesterone was 0.45 times less likely of being infertile (OR=0.451; 95%CI [0.278–0.668], *p*=0.0003).

Table 1: Socio-demographic and clinical Characteristics of participants

BMI categories: underweight < 18 kg/m^2; Normal weight = 18-25Kg/m^2; Overweight= 24-30Kg/m^2; Obese >30 Kg/m^2

Variables	Levels	Cases		Control		*p-value*
		Frequency (n = 86)	Percentage (%)	Frequency (n = 40)	Percentage (%)	
Age group (years)	20 – 25	13	15.1	13	32.5	0.001
	26 – 30	32	37.2	27	67.5	
	31 – 35	26	30.2			
	>35	15	17.4			
Age at menarche (years)	10 – 13	54	62.8	25	62.5	0.978
	14 – 17	32	37.2	15	37.5	
Body mass index (BMI)	Underweight	0	0.0	0	0.0	0.508
	Normal	20	23.3	9	22.5	
	Overweight	30	34.9	18	45.0	
	Obesity	36	41.9	13	32.5	
Occupation	Artisan	28	32.6	15	35.5	0.812
	Business	21	24.4	9	22.5	
	Student	12	14.0	9	22.5	
	Jobs with salary	25	29.1	7	17.5	

Table 2: The distribution of respondents according to LH, FSH, progesterone and oestradiol

Hormones	Levels	Cases		Control		*p-value*
		Frequency (n = 86)	Percentage (%)	Frequency (n = 40)	Percentage (%)	
FSH [2 – 10 IU/L]	Low	0	0.0	0	0.0	<0.0001
	Normal	32	37.2	34	85.0	
	High	54	62.8	6	15.0	
LH [5 – 25 IU/L]	Low	14	16.3	3	7.5	0.4007
	Normal	68	79.1	37	92.5	
	High	4	4.7	0	0.0	
Oestradiol [100 – 400 pg/mL]	Low	4	4.7	1	2.5	0.0190
	Normal	68	79.1	39	97.5	
	High	14	16.3	0	0.0	
Progesterone [4 – 25 ng/mL]	Low	52	60.5	3	7.5	<0.0001
	Normal	28	32.6	35	87.5	
	High	6	7.0	2	5.0	

FSH: Follicle stimulating hormone; LH: Luteinizing hormone.

Table 3: Distribution of study participants according to hormonal and clinical parameters

Variables		Hormonal and Clinical Parameters				*p-value*
Hormones	Group	Mean ±SD	95 % CI		Median	
			Lower	Upper		
FSH (IU/mL)	Cases	12.47 ± 5.47	11.30	13.64	11.03	<0.0001
	Controls	8.88 ± 1.50	8.40	9.36	8.83	
LH (IU/mL)	Cases	6.55 ± 7.19	7.08	10.16	6.55	0.0001
	Controls	9.57 ± 2.75	8.69	10.45	10.47	
Estradiol (pg/mL)	Cases	251.87 ± 166.8	216.09	287.65	203.50	0.5731
	Controls	199.78 ± 63.52	179.46	220.09	193.50	
Progesterone (ng/mL)	Cases	13.48 ± 5.89	13.11	13.84	13.62	<0.0001
	Controls	6.63 ± 7.23	7.02	10.56	7.22	
Age at menarche (years)	Cases	13.37 ± 1.56	13.04	13.71	13.00	0.8277
	Controls	13.35 ± 1.95	12.72	13.98	13.00	
BMI (kg/m^2)	Cases	30.22 ± 6.01	28.93	31.51	29.51	0.2132
	Controls	29.02 ± 5.11	27.39	30.66	27.97	

FSH: Follicle stimulating hormone; LH: Luteinizing hormone

Table 4: Multivariate analysis for the association between hormonal factors and infertility while controlling for age.

Variable	Beta estimate	OR	95% CI	se	*z*-value	*p*-value
Intercept	-9.896	5.03 10^{-05}	1.70 10^{-08}–0.043	3.710	-2.667	0.0076
Age	0.227	1.255	1.100–1.468	0.073	3.117	0.0018
Log (LH)	-0.894	0.409	0.145–1.102	0.510	-1.752	0.0798
Log (FSH)	3.547	34.715	4.759–451.164	1.150	3.084	0.0020
Log (Progesterone)	-0.796	0.451	0.278–0.668	0.220	-3.617	0.0003
Log (Oestradiol)	-0.156	0.855	0.327–2.326	0.491	-0.318	0.7501

FSH: Follicle stimulating hormone; LH: Luteinizing hormone; Se: Standard error; Log: natural logarithm function ; OR : Odds ratio; CI: Confidence interval

DISCUSSION

Infertility may occur due to various health issues such as oocytes immaturity, blockage in fallopian tube, delayed childbearing, late age marriages, weak endometrial lining of uterus all due to hormone imbalance and lifestyle. In this study, about 60% of the infertile women in the Limbe and Buea Hospitals in Southwest of Cameroon, had abnormally high follicle stimulating hormone and low progesterone which was significant. This is the first report on hormonal abnormalities in infertile women in the study area, which could be exploited in the management of these cases of infertility.

The study revealed that higher levels of serum FSH were frequently observed amongst infertile women as compared to the controls (p = 0.001). This is consistent with the known role of FSH to increase the risk of female infertility by causing primary ovarian insufficiency (POI) also called premature ovarian failure [11]. POI occurs due to follicle dysfunction and follicle depletion, follicular migration defect early in embryogenesis; an early decrease in the primordial follicles; increased follicular death; and altered maturation or recruitment of primordial follicles clinically characterized by oligomenorrhoea or amenorrhoea with increased FSH. Increased FSH in infertile women was also reported in another study in Nigeria [12].

This study also found that infertile women had lower levels of progesterone than controls, resulting in irregular menstruation, which is a major risk of female infertility resulting in oligomenorrhoea, menorrhagia, dysmenorrhoea, and inter-menstrual bleeding or spotting. A drop in progesterone results from absence of ovulation or inability of the corpus luteum to produce an adequate amount of progesterone after ovulation or indicates anovulation. Shamila *et al.* in a survey recorded the

same finding that menstrual cycle irregularity was a common occurrence in infertile females with low progesterone in three study areas and was positively correlated with their infertility [13]. Likewise, a case-control study in South-eastern Iran reported that women with irregular menstruation witness a decrease in progesterone levels, compared to their regular cycle counterparts.

In this study, it was found that the risk of infertility increases with age, and many cases were observed over the age of 35. This agrees with a case-control study conducted in Lusaka, Zambia, by Kalima-Munalula *et al.*, who found a significant association between age and female infertility [14]. Increase in age decreases fertility as in the age group 26 – 35 years recorded in this study. Decreased fecundity with increasing age has long been recognized from demographic and epidemiological studies, which consistently found that fertility declines as early as in the middle of the third decade. The biological basis of this decline is attributed to decrease in the number of oocytes from birth to menopause, the quality of existing oocytes and sexual intercourse frequency which declines with age as well.

Menarche is delayed by genetic factors, under-nutrition, hard physical exercise, psychological factors (anorexia nervosa) or chronic general disease, such as heart disease or tuberculosis [15]. These factors may affect not only the menarche but also subsequent infertility [3, 10]. Such factors may also have caused the difference in the infertility rates in the groups with menarche before and after the age of 18. The findings of this study suggest that age at menarche up to 17 years had no significant effect on infertility. In this study, only age at menarche and age of study participant at presentation with infertility were associated with infertility due to hormonal abnormalities whereas BMI and occupation were not. However, other studies have reported several other related factors including dysmenorrhoea, abortion and BMI which may alter hormonal balance and compromise fertility [9, 16, 17].

CONCLUSION

According to the findings of this study, abnormally high levels of follicle stimulating hormones (FSH) and low progesterone are the hormonal abnormalities that may contribute to infertility in affected women in Southwest Cameroon. Furthermore, age atmenarche and biological age are other factor associated with infertility the hormonal abnormalities. Additional research into the pathophysiology of infertility and the identification of other contributing factors may clarify the specific roles of these hormones and provide curative and preventive perspectives for these women.

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