

ORIGINAL ARTICLE

**Lipid Profile in Subfertile Clients with Premature Ovarian Failure:
University of Ilorin Teaching Hospital Experience***I.M AbdulAzeez^{1*}, S.A Biliaminu¹, A.B Okesina¹, A.W.O Olatinwo², L.O Omokanye³*¹*Departments of Chemical Pathology and Immunology, ²Departments of Obstetrics and Gynaecology,*³*Departments of Assisted Reproductive Therapy Unit, University of Ilorin, Ilorin, Kwara State, Nigeria***Abstract:**

Background: Premature Ovarian Failure (POF) is associated with a higher incidence of cardiovascular events later in life. Concurrent with the ages of menopausal transition, a shift in lipid profile takes place. The increased burden may be mediated by a worsening of cardiovascular risk factors, such as lipids, corresponding with the loss of ovarian function. **Aim and Objectives:** To investigate serum lipid and hormonal levels in women with premature ovarian failure and compare with those of apparently healthy women of similar age. **Material and Methods:** The study was a cross-sectional one in which serum fasting Total Cholesterol (TC), Triglycerides (TG), High Density Lipoprotein Cholesterol (HDL-C) and Low Density Lipoprotein Cholesterol (LDL-C) levels were measured in 50 women with POF and compared with 40 age matched control. Serum hormonal profiles were compared with lipid profiles and biomarkers of atherogenic index were assessed. **Results:** Women with POF present with statistically significant elevations in the mean values of serum FSH and LH, when compared with those of controls ($p < 0.001$), while there were significant decrease in mean levels of serum prolactin, progesterone, testosterone and oestradiol when subjects were compared with controls ($p < 0.001$). There were statistically significant elevations in serum total cholesterol, triglycerides, HDL-C and LDL-C, in premature ovarian failure subjects when compared with controls ($p < 0.001$). There was statistically significantly difference when mean values of artherogenic index and Castelli ratio II of subjects were compared with those of controls. **Conclusion:** Loss of ovarian function at a very young age (POF) was characterized with subtle changes

in the serum lipid profile (higher TC, TG, HDL-C, and LDL-C levels). It also shows that atherogenic index and Castelli ratio II are better tools for assessment of atherogenicity than CHD risk ratio and Castelli ratio I in patients with POF.

Keywords: Lipid profile, Atherogenicity, Premature Ovarian Failure

Introduction:

Premature Ovarian Failure (POF) is classically defined as 4–6 months of amenorrhea in women under the age of 40 years associated with menopausal level of serum gonadotropins (FSH > 30 U/l) and hypoestrogenism and is also referred to as hypergonadotropic hypogonadism.

Depending on the age of onset, the disorder can manifest as primary amenorrhea without menarche or secondary amenorrhea after the pubertal development [1, 2]. Premature ovarian failure affects approximately: one in 10,000 women by age 20; one in 1,000 women by age 30; one in 100 women by age 40 [3]. The familial form of POF is rare, representing 4 to 31% of all cases of premature ovarian failure [4-6].

Premature ovarian insufficiency is not the same as premature menopause since around 50% of affected women still experience unpredictable and intermittent ovarian function for many years [7, 8]. This is why some clinicians prefer to use the term Premature Ovarian Dysfunction (POD) in an attempt to reflect the potential reversible nature of

this condition and avoid the idea of failure [9]. Given that no term is perfect, probably the ongoing use of premature ovarian failure until an international consensus is reached, is the best option. Cardiovascular diseases represent the world's leading cause of death among women [10]. An association between early menopause and increased mortality from cardiovascular disease has been established for many years [11] with an estimated 80% increase risk of mortality from ischaemic heart disease in those with menopause under the age of 40 compared with those with menopause at 49–55 [12].

The Danish Nurses cohort study showed that the risk of ischaemic heart disease was greater in premature ovarian failure if of surgical rather than spontaneous nature [13].

Impaired ovarian function is thought to cause increased atherosclerosis progression based on non-human primate models [14] and angiographic studies of estrogen deficiency of hypothalamic nature [15]. Women with premature ovarian failure have been demonstrated to have impaired endothelial function which is often considered as a precursor to atherosclerosis [16]. Reduced endogenous estrogen has also been associated with adverse effects on lipid profile (increased triglycerides, reduced high-density lipoprotein cholesterol) [17]. Furthermore, reduced ovarian reserve, as reflected by elevated serum FSH on day 3 of the menstrual cycle, is associated with increased cholesterol and low-density lipoprotein cholesterol [18], suggesting that factors other than estrogen deficiency may alter cardiovascular risk in premature ovarian failure. The aim of this study was to investigate serum lipid and hormonal levels in women with premature ovarian failure and compare with those of apparently healthy women of similar age, to allow development of evidence-

based management guidelines and improve understanding of the long-term consequences.

Material and Methods:

This study was a cross sectional one, done between April 2016 and October 2016 at the University of Ilorin Teaching Hospital Assisted Reproductive Unit Ilorin, Kwara state; Nigeria. Ethical approval was gotten from the Ethical committee of the hospital.

A total of 50 female clients with premature ovarian failure that constituted a subset of sub-fertile patients attending the facility were recruited for the study. Age ranged between 18 and 40 years, while 40 healthy women matched for age with the patients were recruited as controls. The subjects' results of serum hormonal profile (LH, FSH, prolactin, progesterone, estradiol), were analyzed using Accubind ELISA kits, TC were estimated by Cholesterol Oxidase Method [19]. High Density Lipoprotein Cholesterol (HDL-C) and Low Density Lipoprotein Cholesterol (LDL-C) were also estimated by enzymatic method while triglycerides were estimated using glycerol-3 phosphate oxidase method [20] using commercial kit by Agappe Diagnostics Ltd. The absorbance of samples and standards were measured against reagent blank using Jenway 6300 spectrophotometer at 505nm. Other descriptive parameters and information were extracted from their hospital folders.

The atherogenic ratios were calculated as follows:

Coronary Heart Disease Risk Ratio (CHD-RR) = HDL-C/TC

Atherogenic Index of Plasma (AIP) = $\log \text{ TG} / \text{HDL-C}$

Castelli's Risk Ratio (CRR-I) = TC/HDL-C

Castelli's Risk Ratio (CRR-II) = LDL-C/HDL-C

Statistical analysis was done using Statistical Package for Social Science (SPSS version 20.0) software programme. Results were expressed as means± SD. Paired sample t-test was used to compare means of results, where appropriate p-values < 0.05 were considered statistically significant.

Results:

There was no statistically significant difference when the mean age of POF patients were compared with that of controls, 26.4±5.2 years and 26.5±5.5 years respectively with p-value of 0.663 (Table1). Statistical significant elevations were observed in the mean values of FSH and LH, in subjects (23.0±15.0 mIU/ml, 27.3±38.8 mIU/ml respectively) than in controls (7.3± 2.8 mIU/ml, 4.9 ±1.8 mIU/ml) respectively with p-value less than 0.001 (Table1). However, there was significant decrease in mean serum levels of prolactin, progesterone, oestradiol and testosterone in the study group (13.7± 7.0 ng/ml, 2.2±1.8 ng/ml, 101.8 ±42.3 pg/ml and 0 ± 0.13 ng/ml) than in controls (14.2±2.5 ng/ml, 4.9 ±5.4 ng/ml, 138.0±84.0 pg/ml

and 0.31±0.07ng/ml) respectively with p-value of 0.000. (Table1). In the serum lipid profile, significant elevations were observed in the mean values of Total Cholesterol (TC), Triglyceride (TG), HDL-C and LDL-C, (5.8±1.5 mmol/L, 2.0±1.0 mmol/L, 2.6±0.9 mmol/L, and 1.8±0.5 mmol/L) in premature ovarian failure subjects when compared with controls (3.5±3.5 mmol/L,1.0±0.2 mmol/L, 1.3±0.3 mmol/L, and 1.3±0.2 mmol/L) respectively with p-value of less than 0.001 (Table 2).

There was no statistically significant difference when mean coronary heart disease risk ratio and Castelli ratio I of cases (0.41±0.08, 2.39±0.57) were compared to those of controls (0.36±0.09, 2.88±0.55) with p-values of 0.960 and 0. 253 respectively while there was statistically significantly difference when mean values of atherogenic index and Castelli ratio II of cases (0.106±0.224, 0.73±0.17) were compared with those of controls (0.111±0.072, 0.59±0.44) with p-values of 0.000 respectively (Table 3).

Table 1: Comparison of Mean Values of Fertility Profile in Premature Ovarian Failure Cases and Controls

Variables	Study Group (N=50) Mean ± SD	Control Group (N=40) Mean ± SD
Age (Years)	26.4 ± 5.2	26.4 ± 5.5 ^{NS}
FSH (mIU/ml)	23.0 ± 15.0	7.3 ± 7.8***
LH (mIU/ml)	27.3 ± 38.8	4.9 ± 1.8***
Prolactin (ng/ml)	13.7 ± 07.0	14.2± 2.5***
Progesterone (ng/ml)	2.2 ± 01.8	4.9± 5.4***
Eoestradiol (pg/ml)	101.8± 42.3	138.0±84.3***
Testosterone (ng/ml)	0.29±0.13	0.31± 0.07***

***- P <0.001, NS- Not Significant

Table 2: Comparison of Mean Values of Lipid Profile In Premature Ovarian Failure Cases and Controls

Variables	Study Group (N=50) Mean ± SD	Control Group (N=40) Mean ± SD
TC (mmol/L)	5.8± 1.5	3.5± 3.5***
TG (mmol/L)	2.0± 1.0	1.0± 0.2***
HDL-C (mmol/L)	2.6 ± 0.9	1.3± 0.3***
LDL-C (mmol/L)	1.8 ± 0.5	1.3± 0.2***

***- $P < 0.001$, NS- Not Significant

Table 3: Comparison of Mean Values of Biomarkers of Atherogenicity in Premature Ovarian Failure Cases and Controls

Variables	Study Group (N=50) Mean ± SD	Control Group (N=40) Mean ± SD
CHD-RR	0.41± 0.08	0.36± 0.09 ^{NS}
Atherogenic index	0.10± 0.224	0.11± 0.072***
Castelli ratio I	2.39 ± 0.57	2.88± 0.55 ^{NS}
Castelli ratio II	0.73± 0.17	0.59± 0.44***

***- $P < 0.001$, NS- Not Significant

Discussion:

POF has some important clinical implications as early attenuation of sex steroids in POF has been associated with cardiovascular diseases such as myocardial infarction and stroke [21, 22]. Large number of studies investigating the effects of menopause on cardiovascular outcomes is currently available, but little is known about the cardiovascular effects of POF in young women. Cases of POF in our study presented with abnormalities in lipid profile, but the results were conflicting regarding particular lipoproteins. While in our study, there was elevated serum TC,

TG, HDL-C and LDL-C as against some studies which showed significantly higher TG levels and lower HDL cholesterol levels in comparison to controls [23]. In a study done in new Delhi, about 78% of their subjects had low HDL-C while about 22% had high HDL-C making overall HDL-C to be lower in that particular study[24]. The higher overall mean HDL-C in our study might not be unconnected with the fact that about 45% of our subjects had elevated HDL-C while 55% had lower value. Finding the mean HDL-C in our subjects eventually got tilted towards being high.

This is also responsible for low CHD-RR in our subjects when compared to our control. Another study revealed significantly higher TC and LDL-C levels in POF patients than in the controls [26]. Recently, a study reported increased TC and HDL-C but presented similar levels of LDL-C, and TG in POF women as in the controls [27]. Even though there are conflicting data regarding lipid profile in POF women when compared with the controls, the overall cardiovascular risk in POF women seems to be significantly increased as shown by atherogenic index and Castelli II ratio. The risk of mortality from ischaemic heart disease has been shown to be approximately 80 % increased in the POF women when compared to women with menopause at 49–55 years [12]. According to expert opinion, women with premature ovarian insufficiency should be advised on how to reduce cardiovascular risk factors by not smoking, by taking regular exercise and maintaining a healthy weight to reduce the risk of premature death. The cardiovascular evaluation should consist of monitoring annually blood pressure, weight and smoking status. However the chance for

spontaneous pregnancy is very low; therefore, oocytes donation is the best option for fertility. Due to the risk of psychological problems, patients should be advised to obtain psychological help. Sexual dysfunction should be managed by proper counseling, estrogen replacement and androgen supplementation in chosen cases. Vaginal atrophy may be improved by the use of topical estrogen and lubricants. According to expert opinion, the neurological well-being should be supported by healthy lifestyle interventions as well as estrogen replacement.

Conclusion:

Loss of ovarian function at a very young age (POF) leads to some degree of changes in the lipid profile as obtained in previous studies. We therefore recommend that lipid profile as well as other tools of atherogenicity be estimated and holistically looked into to ensure early medical intervention in reducing to the barest minimum CVD and mortality associated with dyslipidaemia in clients presenting with premature ovarian failure.

References

1. van Noord PA, Dubas JS, Dorland M, Boersma H, te Velde E. Age at natural menopause in a population-based screening cohort: the role of menarche, fecundity, and lifestyle factors. *Fertil Steril* 1997; 68(1):95-102.
2. Nelson LM. Clinical practice. Primary ovarian insufficiency. *N Engl J Med* 2009; 360: 606-14.
3. Santoro N. Mechanisms of premature ovarian failure. *Ann Endocrinol* 2003; 64: 87-92.
4. Timmreck LS, Reindollar RH. Contemporary issues in primary amenorrhea. *Obstet Gynecol Clin North Am* 2003; 30(2):287-302.
5. Coulam CB, Adamson SC, Annegers JF. Incidence of premature ovarian failure. *Obstet Gynecol* 1986; 67(4):604-6.
6. Conway GS, Kaltsas G, Patel A, Davies MC, Jacobs HS. Characterization of idiopathic premature ovarian failure. *Fertil Steril* 1996; 64(2):337-41.
7. Welt CK. Primary ovarian insufficiency: a more accurate term for premature ovarian failure. *Clin Endocrinol (Oxf)* 2008; 68: 449-09.
8. Zhao H, Chen ZJ. Genetic association studies in female reproduction: from candidate-gene approaches to genom-wide mapping. *Mol Hum Reprod* 2013; 19(10): 644-54.
9. Bertini V, Viola D, Vitti P, Simi P, Valetto A. An idic(15) associated with POF (premature ovarian failure): molecular cytogenetic definition of a case and review of the literature. *Gene* 2012; 503(1): 123-5.

10. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics–2015 update: a report from the American Heart Association. *Circulation* 2015;131(4): e29-2
11. Gordon T, Kannel WB, Hjortland MC, McNamara PM. Menopause and coronary heart disease. The Framingham Study. *Ann Intern Med* 1978; 89(2):157-61.
12. Jacobsen BK, Knutsen SF, Fraser GE. Age at natural menopause and total mortality and mortality from ischemic heart disease: the Adventist Health Study. *J Clin Epidemiol* 1999; 52(4): 303-7
13. Løkkegaard E, Jovanovic Z, Heitmann BL, Keiding N, Ottesen B, Pedersen AT. The association between early menopause and risk of ischaemic heart disease: influence of Hormone Therapy. *Maturitas* 2006; 53(2): 226-3.
14. Clarkson TB. Estrogen effects on arteries vary with stage of reproductive life and extent of subclinical atherosclerosis progression. *Menopause* 2007; 14(3 Pt 1):373-84
15. Bairey Merz CN, Johnson BD, Sharaf BL, Bittner V, Berga SL, Braunstein GD, et al. Hypoestrogenemia of hypothalamic origin and coronary artery disease in premenopausal women: a report from the NHLBI-sponsored WISE Study. *J Am Coll Cardiol* 2003; 41(3):413-9.
16. Kalantaridou SN, Naka KK, Papanikolaou E, Kazakos N, Kravariti M, Calis KA, et al. Impaired endothelial function in young women with premature ovarian failure: normalization with hormone therapy. *J Clin Endocrinol Metab* 2004; 89(8):3907-13.
17. Knauff EA, Westerveld HE, Goverde AJ, Eijkemans MJ, Valkenburg O, van Santbrink EJ, et al. Lipid profile of women with premature ovarian failure. *Menopause* 2008; 15(5):919-23.
18. Chu MC, Rath KM, Huie J, Taylor HS. Elevated basal FSH in normal cycling women is associated with unfavorable lipid levels and increased cardiovascular risk. *Hum Reprod* 2003; 18(8):1570-3.
19. Burtis CA, Ashwood ER, Bruns DE. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 5th ed. Philadelphia, PA: WB Saunders; 2013:768-9.
20. Burtis CA, Ashwood ER, Bruns DE. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 5th ed. Philadelphia, PA: WB Saunders; 2013:769.
21. van der Schouw YT, van der Graaf Y, Steyerberg EW, Eijkemans JC, Banga JD. Age at menopause as a risk factor for cardiovascular mortality. *Lancet* 1996; 347(9003):714-8.
22. Wellons M. Cardiovascular disease and primary ovarian insufficiency. *Semin Reprod Med* 2011; 29(4):328-41.
23. Knauff EA, Westerveld HE, Goverde AJ, Eijkemans MJ, Valkenburg O, van Santbrink EJ, et al. Lipid profile of women with premature ovarian failure. *Menopause* 2008; 15(5):919-3.
24. Tehrani FR, Erfani H, Cheraghi L, Tohidi M, Azizi F. Lipid profile and ovarian reserve status: a longitudinal study. *Hum Reprod* 2014; 29(11): 2522-9.
25. Gulhan I, Bozkaya G, Uyar I, Oztekin D, Pamuk BO, Dogan E. Serum lipid levels in women with premature ovarian failure. *Menopause* 2012; 19(11):1231-4.
26. Ates S, Yesil G, Sevket O, Molla T, Yildiz S. Comparison of metabolic profile and abdominal fat distribution between karyotypically normal women with premature ovarian insufficiency and age matched controls. *Maturitas* 2014; 79(3):306-10.

***Author for Correspondence:** Dr. AbdulAzeez, Ishola Musbau, Department of Chemical Pathology and Immunology, University of Ilorin, Ilorin, Nigeria. Email: abdulazeemusbau@yahoo.com, Cell: +2347031621047