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Original Research Article

## Impact of premature ovarian insufficiency on cardiovascular health

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### ABSTRACT

**Background:** The objectives of the study were to identify the causes of premature ovarian insufficiency (POI) and to assess the severity of menopausal symptoms as well as the impact on cardiovascular health in these patients.

**Methods:** Authors did a cross sectional case control study with 100 cases and 100 age matched controls. Women <40years of age with amenorrhoea >4months and FSH >25mIU/ml were identified with POI. Women <40years with normal cycles were the controls. Causes were identified from medical records and menopausal symptoms were categorized using menopause rating score questionnaire. Hypercholesterolemia ( $\geq 200$ mg/dl), hypoalbuminemia ( $< 3.5$ g/dl) and high sensitive C reactive protein (HS-CRP  $\geq 3$ mg/dl) were assessed as the early markers of coronary artery disease. Statistical methods included Chi square test and logistic regression analysis. P value <0.05 was considered significant.

**Results:** 64% of the patients were between 31-40 years. 66% of them were into menopause for <5 years. The cause was idiopathic in 62%. 91% had no or minimal menopausal symptoms. Hypoalbuminemia (6 versus 1, 95% CI 1.8-2.4, OR 2.1, p=0.01) and hypercholesterolemia (75 versus 51, 95%CI 2.5-3.1, OR 2.8, p= 0.001) were significantly high in cases. HS-CRP was not found to be different between the groups (59 versus 49, OR 1.5, 95%CI 0.8-2.6, p=0.2).

**Conclusions:** In majority with POI the cause is idiopathic and menopausal symptoms are minimal. Hypoalbuminemia and hypercholesterolemia, markers of coronary artery disease, were significantly elevated in POI. Early screening for these variables within 5 years of menopause would reduce the cardiovascular mortality in these patients.

**Keywords:** Cardiovascular disease, Hypercholesterolemia, Hypoalbuminemia, Premature ovarian insufficiency

### INTRODUCTION

Hypergonadotropic hypogonadism before the age of forty affects 1-2% of women. It occurs in 1 in 10,000 women by 20years, 1 in 1000 women by 30 years and reaches 1 in 100 by 40 years.<sup>1</sup> ESHRE (European Society for Human Reproduction and Embryology) 2016 recommends the following diagnostic criteria for premature ovarian insufficiency (POI): (a) oligo/amenorrhoea for at least 4 months, and (b) an elevated follicle stimulating hormone (FSH) >25IU/l on 2 occasions more than 4 weeks apart.<sup>2</sup> POI needs greater

attention in the wake of its increased morbidity.<sup>1</sup> Minor morbidities includes mood swings, vasomotor symptoms, sexual dysfunction, lower urinary tract symptoms and musculoskeletal issues. But in the long run they tend to develop life threatening issues like osteoporotic fractures and coronary artery disease.<sup>1</sup>

The hypoestrogenic state accounts for all the morbidities except for reduced libido which is due to low androgen levels. All cause mortality has also been found to be higher in POI from coronary artery disease (RR-1.09), respiratory disease (RR 1.19) and genitourinary disease

(RR -1.39).<sup>1</sup> In view of the long-term health consequences of POI, efforts should be made to identify women with POI and commence interventions to reduce the associated morbidity and mortality. There is limited literature available in this regard from India. In the light of this we report a clinical study of the causes of POI, severity of menopausal symptoms in them as well as the impact of POI on cardiovascular health.

## METHODS

This is a cross sectional case control study conducted in a tertiary referral centre in South India from 1<sup>st</sup> April 2016 to 30<sup>th</sup> April 2017. The study was approved by the institutional review board and ethics committee. Informed consent was obtained prior to inclusion in the study. One hundred consecutive cases of POI were recruited from subjects who attended menopause and general gynaecology outpatient clinics. The inclusion criteria were women <40 years with oligo/amenorrhoea for >4 months and FSH >25mIU/ml.<sup>2</sup> Women <40 years with normal menstrual cycles were taken as controls. Controls were chosen by 1- to -1 age matching with the cases. These included asymptomatic volunteers who were staff of our hospital and women who attended outpatient clinic for other gynaecological problems. Women on menopausal hormone therapy and previously diagnosed with coronary artery disease were excluded. Primary objectives were to assess the causes and severity of menopausal symptoms in POI and its impact on cardiovascular health. Sample size was calculated based on a study done by Gulhan et al using nMaster 2.0 software.<sup>3</sup> To compare the proportion of hypercholesterolemia between cases and controls, the number needed was 100 in each group to give a power of 80% with alpha error of 5%.

Each participant underwent history taking, physical examination, menopause rating score estimation and blood investigations. Age of the patient, parity, domicile, age at menopause, duration of menopause, the cause of menopause, and the socioeconomic score utilizing modified Kuppuswamy scale, medical, surgical and family history and degree of physical activity using International Physical Activity Questionnaire were recorded in the history.<sup>4,5</sup> The cause of menopause was identified from the previous medical records of the patient. Those with no identifiable cause were grouped under idiopathic POI. A simple physical examination was done to check the height, weight, body mass index and waist circumference. Height and weight were measured using wall mounted stadiometer and electronic weighing scale which were calibrated on a weekly basis. Waist circumference measurement was done using a calibrated tape midway between the lowest rib margin and the iliac crest. To assess the severity of menopausal symptoms we used a previously validated questionnaire which looked at 11 menopausal symptoms - hot flushes, palpitation, depressive mood, irritability, anxiety, physical and mental exhaustion, sexual problems, bladder problems,

dryness of vagina and musculoskeletal symptoms based on which menopause rating score was calculated for each subject.<sup>6</sup>

All cases were recruited after documenting FSH >25mIU/ml. Serum parameters (our lab standardization values are given) done for each patient included fasting (70-110mg/dl) and 2 hour postprandial sugars (<140mg/dl), lipid profile (total cholesterol<200mg/dl, triglyceride<150mg/dl, LDL<100mg/dl, HDL>60mg/dl), creatinine (0.5-1.1mg/dl), serum albumin (3.5-5.0g/dl) and high sensitive C reactive protein (HS-CRP <3mg/dl). All the biochemical parameters excluding FSH were done for the controls.

Authors used hypercholesterolemia (total cholesterol  $\geq$ 200mg/dl), hypoalbuminemia (<3.5g/dl) and raised high sensitive C reactive protein (HS-CRP  $\geq$ 3mg/dl) as early markers of CAD risk.<sup>7,8</sup> Metabolic syndrome was assessed as a confounder for CAD risk. Metabolic syndrome was identified in patients with waist circumference  $\geq$ 80cm with any two of the following four factors-systolic blood pressure (BP)  $\geq$ 130mm of Hg, diastolic BP  $\geq$ 85mm of Hg, or treatment of previously diagnosed hypertension, fasting plasma glucose  $\geq$ 100mg%, previously diagnosed type 2 diabetes, serum triglycerides  $\geq$ 150mg/dl, high density lipoprotein HDL <50mg/dl or specific treatment for lipid abnormality.<sup>9</sup> HS-CRP is a marker of atherosclerosis which in turn would lead to CAD. Authors have used chemoluminescent immunoassay to detect HS-CRP in 1 in 20 dilution. The cut off taken was  $\geq$ 3mg/dl according to our lab standardization.

## Statistical analysis

The data was analysed using SPSS 16.0 software. Descriptive statistics were calculated to describe the measured variables of cases and controls. Age matching was accounted in the analysis by using conditional logistic regression. Chi-square test was used to test the association between the disease status and outcome variables. The logistic regression analysis was used to do the risk estimate and its 95% CI. A p value <0.05 was considered as statistically significant.

## RESULTS

Authors evaluated 136 women with premature ovarian insufficiency. Twenty four women were excluded due to prior hormone therapy or CAD. Twelve women were lost for follow up. One hundred eligible women and 100 age matched controls were included in the study. Demographic factors (Table 1) showed no significant difference between the groups except hypertension (p=0.04). 7% of the patients were aged <20 years, 20-30 years were 29% and 31-40 years were 64%. Duration of menopause was <5 years in 66%, 5-10 years in 20% and  $\geq$ 11 years in 14%. One of the aims of present study was to delineate the causes of menopause. In 62 patients the

cause was idiopathic. Surgical menopause occurred in 24, chemotherapy and autoimmune diseases was the cause in 8 and 6 women respectively. Menopause rating score assessment found 37 with no menopausal symptoms, 54 with mild symptoms and 9 with moderate symptoms. None had severe symptoms.

**Table 1: Demographic variables.**

	Cases (n=100)	Controls (n=100)	P value
Mean age	36.2±7.5	34.9±5.5	0.3
Mean BMI	24.9±4.8	25.6±4.9	0.5
Diabetes mellitus	8	5	0.4
Hypertension	15	6	0.04

CAD risk in POI was estimated based on hypercholesterolemia and hypoalbuminemia (Table 2).

Total cholesterol >200mg/dl (75 vs. 51, OR 2.84, 95% CI 2.5-3.1, p=0.001), low density lipoprotein (LDL) >100mg/dl (60 VS 41, OR 2.1, 95% CI 1.2-3.8, p=0.008) and triglyceride >150 mg/dl (24 vs. 12, OR 2.2, 95% CI 1.0-4.7, p=0.04) levels were found to be significantly elevated in POI.

Controls had lower HDL levels compared to cases, but the difference was not significant (69 vs. 77, OR-0.6, 95% CI 0.4-0.9, p=0.2). Women with POI had significant hypoalbuminemia (6 vs. 1, OR 2.1, 95%CI 1.8-2.4, p=0.01). HS-CRP, a marker of chronic low-grade inflammation, 1.5 was found elevated in cases than controls but the difference was not statistically significant (59 vs. 49, OR, 95% CI 0.8-2.6, p= 0.2) (Table 2). So, authors infer that atherosclerotic changes may not have started in our cases, majority of whom are <5 years into menopause. Hence hypercholesterolemia and hypoalbuminemia seem to be important early CAD risk markers in POI.

**Table 2: Coronary artery disease (CAD) risk assessment.**

CAD Risk factors	Cases (n=100)	Controls (n=100)	OR	95%CI	p value
Serum albumin < 3.5g/dl	6	1	2.1	1.8-2.4	0.01
Total cholesterol ≥200mg/dl	75	51	2.84	2.5-3.1	0.001
HDL<50mg/dl	69	77	0.6	0.4-0.9	0.2
Triglyceride ≥150mg/dl	24	12	2.2	1.0-4.7	0.04
LDL ≥100mg/dl	60	41	2.1	1.2-3.8	0.008
HS-CRP> 3mg/dl	59	49	1.5	0.8-2.6	0.2

Confounders of CAD risk were similar between the groups except hypertension (15 vs. 6, p=0.04). More cases were found to be hypertensive (Table 3) probably due to endothelial changes secondary to hypercholesterolemia and hypoalbuminemia. Metabolic syndrome was also assessed as a confounder but did not differ between the groups (41vs 32, OR 1.2, 95%CI 0.9-1.4, p=0.2).

**Table 3: Confounders for CAD risk.**

	Cases	Controls	p value
BMI >25	44	52	0.3
Diabetes mellitus	8	5	0.4
Hypertension	15	6	0.04
Family history of CAD	1	4	0.4
Metabolic syndrome	41	32	0.2

**DISCUSSION**

The incidence of cardiac events has been found to be higher after natural menopause and POI.<sup>10</sup> Present study evaluates the causes of POI, severity of menopausal

symptoms and markers of CAD risk in a group of Indian women with POI as compared to age matched healthy controls .We have also tried to assess how many years after menopause should we start screening for CAD risk in POI and what are the useful strategies.

POI was first described in 1942 by Albright et al and has, since then, been described by various names and definitions.<sup>10</sup> POI is a clinical syndrome of loss of ovarian activity before the age of 40 years.<sup>11</sup> This study could not comment on the incidence of POI since authors have chosen cases based on strict exclusion criteria. Authors found that in 62% of POI the cause was idiopathic, 24% had surgical menopause and cancer chemotherapy accounted for 8%. Majority of our cases (64%) were between 31-40 years of age. In 66% the duration of menopause was <5 years. Majority (91%) had only minimal to mild menopausal symptoms probably due to hypoestrogenemia from the time of menarche. As a result, majority are not seeking medical care. This aspect has not been addressed in previous studies.

Women with POI have been proven to be at high risk for CAD.<sup>12</sup> The predisposing factors include endothelial dysfunction, autonomic dysfunction, abnormal lipid

profile, insulin action disturbances and metabolic syndrome. Endothelial dysfunction, a known sequel to hypoestrogenemia, could be the initiating event in atherosclerosis.<sup>13</sup> Impaired endothelial function is evident in POI as early as a month following bilateral oophorectomy.<sup>14</sup> Impaired flow mediated dilatation of the brachial artery increased carotid intima media thickness and left ventricular diastolic dysfunction are common in these women. A decrease in circulating endothelial progenitor cells has also been documented in POI.<sup>15</sup> In addition they have impaired baroreceptor sensitivity and reduced heart rate variability compared to healthy controls.<sup>16</sup> Menopausal hormone therapy (MHT) for 6 months has shown to improve the flow mediated dilatation by 2.4- fold, to the same level as healthy controls.<sup>17</sup>

CAD has also been attributed to dyslipidemia in POI but there are conflicting results. One study has reported significantly high triglyceride levels and lower HDL cholesterol levels in comparison to controls after correction for age and body mass index (47 POI vs. 60 controls).<sup>12</sup> However this group revealed significantly higher total cholesterol and LDL levels in POI women and a significant negative co-relation between estradiol and total cholesterol levels ( $r=0.291$ ,  $P=0.047$ ). In this study total cholesterol was found to be significantly high among cases (75% vs. 51%,  $p=0.001$ ). Low HDL levels were more in controls (69% vs. 77%;  $p=0.2$ ), but no significant difference was found. Present study evidence supports the previous studies.

Ates et al has reported increased total and HDL cholesterol in POI women with similar levels of glucose, insulin, LDL index, triglyceride index and smoking thus showing a high incidence of metabolic syndrome in POI.<sup>18</sup> Authors could not find a significant difference between the groups in the incidence of metabolic syndrome (41% vs. 32%;  $p=0.2$ ).

Cardiovascular morbidity of POI has also been highlighted by the Multi ethnic study of Atherosclerosis which showed that heart failure was increased by 66% in those undergoing menopause earlier than 45 years compared with women experiencing later menopause with a 4% decrease in risk with every one year increase in age at menopause.<sup>19</sup>

All cause mortality was also found to be more in POI from the Nurse's Health Study and The Mayo Clinic Cohort Study of Oophorectomy and Aging. Particularly, the mortality from ischemic heart disease is approximately 80% more in the POI group compared to women with menopause at 40-55 years.<sup>20</sup> MHT was found to attenuate the mortality risk.<sup>20</sup> Data from our study suggests that hypercholesterolemia might be one of the factors which could initiate endothelial damage and atherosclerosis. Hence early screening for dyslipidemia and use of lipid lowering agents is of utmost importance while considering treatment options in POI.

Hypoalbuminemia is another risk factor for CAD which has not been evaluated in POI. Albumin is a carrier of steroid hormones and its synthesis is stimulated by them.<sup>21</sup> Estrogen deficiency in POI could cause hypoalbuminemia. Several studies have brought out an inverse relationship between serum albumin level and incidence of CAD and stroke in the general population.<sup>22,23</sup> The hazard ratio for CAD is 1.26 for every one standard deviation decrease in serum albumin level.<sup>24</sup> Hypoalbuminemia enhances the production of free radicals from lipid peroxidation systems and inhibits endothelial apoptosis which are the early steps in the atherosclerotic process.<sup>25,26</sup> Present study has shown, for the first time, a significantly high level of hypoalbuminemia (6% vs. 1%, OR 2.1, 95% CI 1.8-2.4,  $p=0.01$ ) in POI.

HS-CRP, a marker of atherosclerosis, has not been previously assessed in women with POI.<sup>27</sup> In this study HS-CRP was found elevated in more cases than controls but did not show any significant difference between the groups (59% vs. 49%, OR 1.5, 95% CI 0.8-2.6,  $p=0.2$ ). So, authors infer that atherosclerotic changes might not have started in majority of our patients (66%) who were into menopause only for <5years (Table 2). Therefore, low serum albumin level and high total cholesterol levels seems to be better early markers of CAD risk in POI before the onset of any inflammatory changes in the arterial walls.

The strengths of present study include the case-control nature with 1-to-1 matching and analysis based on serum values which gives highly objective data. Majority of studied patients were in the first 5 years of POI which has facilitated assessment of early changes after menopause. Drawback was the small sample size and lack of long term follow up. Hypertension was found to be a significant confounder, but it could be a secondary outcome of endothelial changes induced by hypercholesterolemia and hypoalbuminemia.

## CONCLUSION

POI needs greater attention as it increases the morbidity and all cause mortality in comparatively younger women. We found that in majority, the cause of POI is idiopathic. Since menopausal symptoms are only minimal women tend to evade medical care. This study shows significant hypercholesterolemia ( $p=0.001$ ) and hypoalbuminemia ( $p=0.01$ ) as early as 5years into POI.

Hence hypercholesterolemia and hypoalbuminemia prove to be more efficient early markers of CAD compared to HS-CRP. Taking evidence from our cases, serum screening for hypercholesterolemia and hypoalbuminemia should commence early in POI probably within 5 years of menopause. There is a trend for high HS-CRP in cases, but this would need studies with larger sample size for complete evaluation.

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## REFERENCES

- Podfigurna-Stopa A, Czyzyk A, Grymowicz M, Smolarczyk R, Katulski K, Czajkowski K. Premature ovarian insufficiency: the context of long-term effects. *J Endocrinol Invest.* 2016;39:983-90.
- European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI, Webber L, Davies M, Anderson R, Bartlett J, Braat D, et al. ESHRE Guideline: management of women with premature ovarian insufficiency. *Hum Reprod Oxf Engl.* 2016;31(5):926-37.
- 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.
- Singh T, Sharma S, Seetharamiah N. Socio-economic status scales updated for 2017. *Int J Res Med Sci.* 2017; 5(7):3264-3267.
- Maddison R, Ni Mhurchu C, Jiang Y, Vander Hoorn S, Rodgers A, Lawes CMM et al. International Physical Activity Questionnaire (IPAQ) and New Zealand Physical Activity Questionnaire (NZPAQ): A doubly labelled water validation. *Int J Behav Nutr Phys.* 2007; Act 4:62.
- Heinemann LAJ, Potthoff P, Schneider HPG. International versions of the Menopause Rating Scale (MRS). *Health Qual Life Outcomes.* 2003; 1:28.
- Soran H, Adam S, Mohammad JB, Ho JH, Schofield JD, Kwok S, et al. Hypercholesterolaemia - practical information for non-specialists. *Arch Med Sci.* 2018; 14(1):1-21.
- Kim S, McClave SA, Martindale RG, Miller KR, Hurt RT. Hypoalbuminemia and Clinical Outcomes: What is the Mechanism behind the Relationship? *Am Surg.* 2017; 83(11):1220-7.
- Targher G, Bertolini L, Tessari R, Zenari L, Arcaro G. The international diabetes federation definition of the metabolic syndrome independently predicts future cardiovascular events in Type 2 diabetic patients. The valpolicella heart diabetes study. *Diabet Med.* 2006;23(11):1270-1.
- Podfigurna-Stopa A, Czyzyk A, Grymowicz M, Smolarczyk R, Katulski K, Czajkowski K, et al. Premature ovarian insufficiency: the context of long-term effects. *J Endocrinol Invest.* 2016; 39(9):983-90.
- Coulam CB, Adamson SC, Annegers JF. Incidence of premature ovarian failure. *Obstet Gynecol.* 1986;67(4):604-6.
- Atsma F, Bartelink M-LEL, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. *Menopause N Y N.* 2006;13(2):265-79.
- Ross R. Atherosclerosis-an inflammatory disease. *N Eng J Med.* 1999 Jan;340(2):115-26.
- Virdis A, Ghiadoni L, Pinto S, Lombardo M, Petraglia F, Gennazzani A, et al. Mechanisms responsible for endothelial dysfunction associated with acute estrogen deprivation in normotensive women. *Circulation.* 2000;101(19):2258-63.
- Yorgun H, Tokgözoğlu L, Canpolat U, Gürses KM, Bozdağ G, Yapıcı Z, et al. The cardiovascular effects of premature ovarian failure. *Int J Cardiol.* 2013; 168(1):506-10.
- Goldmeier S, De Angelis K, Rabello Casali K, Vilodre C, Consolim-Colombo F, Belló Klein A, et al. Cardiovascular autonomic dysfunction in primary ovarian insufficiency: clinical and experimental evidence. *Am J Transl Res.* 2013;6(1):91-101.
- 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.
- Ebong IA, Watson KE, Goff DC, Bluemke DA, Srikanthan P, Horwich T, et al. Age at menopause and incident heart failure: the Multi-Ethnic Study of Atherosclerosis. *Menopause.* 2014;21(6):585-91.
- Rivera CM, Grossardt BR, Rhodes DJ, Brown RD, Roger VL, Melton LJ, et al. Increased cardiovascular mortality after early bilateral oophorectomy. *Menopause N Y N.* 2009; 16(1):15-23.
- Gierach GL, Pfeiffer RM, Patel DA, Black A, Schairer C, Gill A, et al. Long-term overall and disease-specific mortality associated with benign gynecologic surgery performed at different ages. *Menopause* 2014; N Y N. 21(6):592-601.
- Jefferson DM, Reid LM, Giambrone MA, Shafritz DA, Zern MA. Effects of dexamethasone on albumin and collagen gene expression in primary cultures of adult rat hepatocytes. *Hepatology.* 1985 Jan 1;5(1):14-20.
- Nelson JJ, Liao D, Sharrett AR, Folsom AR, Chambless LE, Shahar E, et al. Serum albumin level as a predictor of incident coronary heart disease: the atherosclerosis risk in communities (ARIC) study. *Am J Epidemiol.* 2000 Mar 1;151(5):468-77.
- Djoussé L, Rothman KJ, Cupples LA, Levy D, Ellison RC. Serum albumin and risk of myocardial infarction and all-cause mortality in the Framingham Offspring Study. *Circulation.* 2002; 106(23):2919-24.
- Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA.* 1998;279(18):1477-82.
- Luoma PV, Näyhä S, Sikkilä K, Hassi J. High serum alpha-tocopherol, albumin, selenium and cholesterol, and low mortality from coronary heart disease in northern Finland. *J Intern Med.* 1995; 237(1):49-54.
- Schnatz PF. The 2010 North American Menopause Society position statement: Updates on screening,

prevention and management of postmenopausal osteoporosis. *Connecticut Med.* 2011 Sep;75(8):485-7.

27. Ahmed SH, Kharroubi W, Kaoubaa N, Zarrouk A, Batbout F, Gamra H, et al. Correlation of trans fatty acids with the severity of coronary artery disease

lesions. *Lipids in health and disease.* 2018 Dec;17(1):52.

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