International Journal of Research in Medical Sciences
Shinde AS et al. Int J Res Med Sci. 2021 Jul;9(7):1929-1934
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20212511

Original Research Article

Evaluation of coronary artery risk factors in premenopausal women (<45 years): a single-center prospective study

Alok Suresh Shinde[1]*, Anand Narendra Shukla[2], Priyadarshini Mahadev Dixit[3]

[1]Consultant and Interventional Cardiologist, Apple Saraswati Multispeciality Hospital, Kolhapur, Maharashtra, India
[2]Professor in Cardiology, U. N. Mehta Institute of Cardiology and Research Centre, Ahmedabad, Gujarat, India
[3]St Joseph Mercy Oakland Hospital, Pontiac, Michigan, United States of America

Received: 26 April 2021
Revised: 30 May 2021
Accepted: 31 May 2021

***Correspondence:**
Dr. Alok Suresh Shinde,
E-mail: docalok1985@gmail.com

ABSTRACT

Background: The present study was designed to evaluate the association of conventional coronary risk factors in the angiographically proven cases of younger women (<45 years) with significant CAD along with clinical profile and coronary angiographic findings.
Methods: This was a hospital-based prospective study conducted at a tertiary-care center in India. A total of 200 premenopausal women (age ≤45 years) who presented with chest pain likely to be of cardiac origin were enrolled. Each patient was subjected to routine clinical investigations, examination of complete lipid profile, follicular stimulating hormone (FSH), luteinizing hormone (LH), and prolactin; and underwent non-invasive cardiac examination and coronary angiography.
Results: Mean age of patients was 39.1±4.98 years. A total of 64 (32%) patients had history of spontaneous abortions and 80 (40%) patients presented with ST-elevated myocardial infarction. Increased FSH, LH and prolactin levels was found in 70 (35%), 20 (10%), and 88 (44%) patients, respectively. Total 196 (98%) patients underwent coronary angiography which revealed presence of significant CAD in 122 (63%) cases and of which 80 patients underwent coronary angioplasty and 12 underwent coronary artery bypass grafting. Of all, 8 death were reported up to the mean follow-up of 11 months.
Conclusions: The study stated that premenopausal females (<45 years) represent a special subgroup where non-conventional risk factors play an important role in occurrence of CAD. So, careful history taking with detailed menstrual and obstetric history should be considered in such group of patients.

Keywords: Follicular stimulating hormone, Prolactin, Premature coronary artery disease, Premenopausal women, Percutaneous coronary intervention

INTRODUCTION

Cardiovascular disease is the leading cause of mortality and morbidity in females. Most of the studies about coronary artery disease (CAD) in young adults describe risk factors and angiographic data predominantly for male subjects. There is a paucity of data concerning CAD in women, particularly young women (<45 years). Though the gap between women and men in terms of incidence and mortality narrows with advancing age, the available data suggest that our concept and understanding of CAD in women are evidently far from complete.

Symptomatic obstructive coronary artery disease is less common in premenopausal women than in men of comparable age and the clinical diagnosis is often difficult

to establish.[1,2] Many risk factors, first documented in males, were lately found to affect the females in similar manner. Women younger than 55 years, have worse prognosis after acute myocardial infarction than their male counterparts, with greater incidence of recurring event and higher mortality.[3] Currently, Indian subcontinent is experiencing rapid increase in the rates of CAD.[4] Studies in Indian subcontinent and subcontinent immigrants in developed countries suggest an earlier onset of aggressive CAD with higher rate of complications and with common cluster of risk factors.[5] Many studies about CAD have excluded women and as a result, a significant lack of information exists regarding risk factors, preventive strategies, diagnostic testing, and treatment of women with CAD. This lack of information is even greater concerning young women.

The present study was designed to define the association of conventional coronary risk factors in the angiographically proven cases of younger women (<45 years) with significant CAD. This study was also aimed to describe clinical profile and coronary angiographic findings of premenopausal women presenting with chest pain.

METHODS

This was a single-centre prospective study conducted at UN Mehta Institute of Cardiology and Research Center, Ahmedabad, India, between November-2016 and March-2018. After the ethical clearance from the institutional ethic committee, 200 premenopausal women of age ≤45 years who presented with chest pain likely to be of cardiac origin were enrolled. The study strictly followed the standard clinical practice guidelines and Declaration of Helsinki. The written informed consent was obtained from each patient. The patients who had congenital heart disease, valvular abnormalities, or subaortic stenosis, myocarditis were excluded. But patients with cardiomyopathy were not excluded if coronary artery disease was suspected.

Patients on oral hypoglycemic drugs, insulin or those having fasting blood sugar >126 g/dl were regarded as having diabetes mellitus. Those with blood pressure >140/90 mmHg taken twice or those on antihypertensive drugs were defined as hypertensives. Waist circumference and hip circumference were measured by a staff nurse at the level of anterior superior iliac spine. A waist circumference >80 cm was considered abnormal. Body mass index (BMI) of 18.0-22.9 kg/m2 was regarded as normal, obesity was defined as BMI >25 kg/m2.Females with history of ischemic heart disease in first degree male relatives of <55 years or in female relatives <65 years were regarded as having history of premature CAD in the family.

Each patient was subjected to routine investigations including complete blood counts, fasting blood sugar, blood urea, serum creatinine, fasting lipid profile, electrocardiogram, and creatine phosphokinase-myocardial band (CPK-MB) and Troponin-I (whenever relevant). These patients were further investigated with echocardiography/doppler study, tread-mill test (TMT) and coronary angiography. We performed lipid profile, lipoprotein(a), apolipoprotein A1 and B, homocysteine, highly sensitive C-reactive protein (hs-CRP), follicular stimulating hormone (FSH), luteinizing hormone (LH), and prolactin. We examined the correlation between FSH level measured at 3rd day of a measure of ovarian reserve and lipid profiles in all patients. A serum FSH level >7 IU/l at 3rd day of menstrual cycle was considered as abnormal.

Fifty percent or more diameter stenosis in any major coronary artery or its major branch (>2.5 mm) was considered as significant CAD and were considered for coronary angioplasty. An attempt was made to follow each patient for at least two years or until death and to determine the course after arteriography and coronary intervention. Clinical records were reviewed, patients or patients' families were contacted by telephone. Death thought to be due to coronary disease, myocardial infarction and arteriographically proved development or progression of coronary obstruction to at least 50% luminal diameter and at least 20% more narrowing than in the original arteriogram were considered coronary events.

Statistical analysis

Data were expressed as frequency (percentage) for categorical variables and as mean±SD for continuous variables. Univariate analysis was performed using Chi-square test and unpaired student's t-test. A probability value of $p<0.05$ was considered as statistically significant. All the analysis were performed using Statistical package for the social sciences (SPSS) (IBM Version 20, California, USA).

RESULTS

Mean age of patients was 39.1±4.98 years with maximum number of patients (n=130) in 40-45 age group. Among all, 140 (70%) presented with typical angina whereas 60 (30%) presented with atypical angina. Dyslipidemia was the most common risk factor found in 156 (78%) patients. A total of 64 (32%) patients had history of spontaneous abortions. The detailed demographic details and baseline characteristics are outlined in Table 1.

Eighty (40%) patients presented with ST-elevated myocardial infarction (STEMI). Among all, 116 (58%) patients had normal echocardiographic findings. Anterior regional wall motion abnormality (RWMA) was observed in 58 (29%) patients, inferior RWMA in 18 (9%), posterior RWMA in 4 (2%), and lateral in RWMA 4 (2%) patients. A total of 48 (24%) patients underwent TMT of which 22 (11%) showed positive results with a sensitivity and specificity of 54% and 69%, respectively. Clinical presentation and diagnostic details are depicted in Table 2.

Table 1: Baseline demographic details.

Variable	Mean±SD/n (%)
Age, years (mean ± SD)	39.1±4.98
Clinical profile	
Typical angina	140 (70)
Atypical angina	60 (30)
Dyspnea	90 (45)
Risk factors	
Diabetes mellitus	50 (25)
Hypertension	96 (48)
Family history of premature CAD	36 (18)
Cerebrovascular accident	4 (2)
Peripheral vascular disease	4 (2)
Dyslipidemia	156 (78)
Oral contraceptive pills	62 (31)
Body mass index	
Underweight	10 (5)
Normal	46 (23)
Overweight	28 (14)
Obese	116 (58)
Waist circumference	120 (60)
Menstrual history	
Regular	116 (58)
Irregular	50 (25)
Dysmenorrhea	8 (4)
Oligomenorrhoea	20 (10)
Menorrhagia	6 (3)
Obstetric history	
History of abortions	64 (32)

CAD: coronary artery disease

Biochemical examination revealed decreased high-density lipoprotein (HDL) cholesterol level in 152 (76%) patients, increased lipoprotein(a) level in 100 (50%), increased triglyceride level in 40 (20%), decreased apolipoprotein A1 in 36 (18%) patients. LDL/HDL ratio was increased in 36 (18%) and non-HDL cholesterol was increased in 22 (11%) patients. Furthermore, hyper-homocysteinemia was found in 46 (23%) patients and raised hs-CRP level was observed in 58 (29%) patients. Increased FSH level was found in 70 (35%), increased LH in 20 (10%), and prolactin was increased in 88 (44%) patients.

Of 200 patients, 196 (98%) patients underwent coronary angiography which revealed presence of significant CAD in 122 (63%), insignificant in 12 (6%), and normal coronary arteries in 62 (31%) patients. Out of 90 single vessel disease patients, left anterior descending artery was involved in 72 (80%) cases, left circumflex artery in 12 (13%) cases, and right coronary artery in 6 (7%) cases.

Among 122 patients with significant CAD, 80 (65.57%) underwent coronary angioplasty i.e. 8 (10%) underwent primary PCI, 42 (52.5%) underwent adhoc PCI at the time of diagnostic cardiac catheterization, and 44 (55%) patients were thrombolysed. Twelve (9.83%) patients were referred for coronary artery bypass grafting and two underwent surgical grafting with mitral valve repair. Rest of the patients opted for medical management due to either financial constraints or non-willingness for revascularization.

Table 2: Clinical and diagnostic characteristics.

Characteristics	n (%)
Clinical presentation	
STEMI	80 (40%)
Anterior wall	58 (72.5%)
Inferior wall	20 (25%)
Posterior wall	2 (2.5%)
Chronic Stable Angina	58 (29%)
NSTEMI	18 (9%)
Unstable Angina	44 (22%)
ECG findings	
Anterior	96 (48%)
Inferior	32 (16%)
Lateral	8 (4%)
Posterior	4 (2%)
Left bundle branch block	4 (2%)
Right bundle branch block	2 (1%)
Normal	54 (27%)
Echocardiographic findings	
Mild LVD	26 (13%)
Moderate LVD	38 (19%)
Severe LVD	20 (10%)
Normal LV function	116 (58%)
Coronary angiography (n=196)	
Significant CAD	122 (63%)
Insignificant CAD	12 (6%)
Normal coronary arteries	62 (31%)
Type of disease	
Single vessel disease	90 (74%)
Double vessel disease	18 (15%)
Triple vessel disease	14 (11%)
Type of vessel involved	
Left anterior descending artery	88 (44.89%)
Left circumflex artery	28 (14.28%)
Right coronary artery	24 (12.25%)
Obtuse marginal-1	6 (3.06%)
Obtuse marginal-2	4 (2.04%)
Left main coronary artery	2 (1.02%)

STEMI: ST elevation myocardial infarction; NSTEMI: non-ST elevation myocardial infarction; ECG: electrocardiogram; LVD: left ventricular dysfunction; and CAD: coronary artery disease

Of 200 patients enrolled in the study, death was reported in 8 cases [4 during first hospitalization and 4 during follow-up (2 in-stent restenosis and 2 reinfarction)] of which 6 were cardiac death and 2 were non-cardiac death. The mean follow-up was of 11 months available for 180 (94.73%) patients.

The correlation of various risk factors and diagnostic parameters in patients with significant CAD (n=122) and non-significant CAD/normal coronaries (n=74) is depicted in Table 3. The difference in prevalence of

hypertriglyceridemia, decreased HDL and increased hs-CRP between significant and insignificant CAD was statistically significant (p <0.05). FSH level measured on 3rd day of menstrual cycle, prolactin levels and history of abortions were correlated in patients with significant and insignificant CAD. The difference in prevalence was not significant for patients with increased FSH and prolactin. Though the history of spontaneous abortions was more frequently found in patients with significant CAD, the difference was not statistically significant. (p=0.0752). Levels of FSH, LH and prolactin in patients based on parity status have been outlined in Table 4.

Table 3: Univariate correlation of various parameters in patients with significant CAD and insignificant/normal coronary arteries.

Parameters	Significant CAD (n=122)	Insignificant CAD/Normal (n=74)	P value
Age, years	38.82±4.43	40.27±4.33	**0.026**
Diabetes, n (%)	38 (30.15)	12 (16.2)	**0.031**
Hypertension, n (%)	54 (44.2%)	42 (56.7%)	0.061
Family history of CAD, n (%)	27 (22.1%)	10 (13.5%)	0.094
Peripheral vascular disease, n (%)	4 (3.3%)	00	-
Oral contraceptives, n (%)	84 (68.9%)	52 (70.3%)	0.483
Menstrual history, n (%)	57 (46.7%)	26 (35.1%)	0.074
History of abortion, n (%)	43 (35.2%)	20 (2.7%)	0.150
BMI, kg/m^2	26.11±4.96	26.33±4.31	0.748
Waist circumference, cm	88.27±11.19 (n=118)	90.06±10.74 (n=70)	0.284
Random blood sugar, mg/dL	157.57±87.16	127.19±77.31	**0.014**
Serum creatinine, mg/dL	0.72±0.12	0.74±0.20	0.464
Blood urea, mg/dL	25.31±9.67	23.05±7.21	0.083
Cardiac Troponin-I	7.94±16.03 (n=54)	6.57±15.21 (n=30)	0.703
CPK-MB, units/L	62.40±86.21 (n=84)	68.49±113.21 (n=28)	0.766
Total cholesterol, mg/dL	151.58±47.24	148.70±34.90	0.650
Triglycerides, mg/dL	137.81±97.10	95.85±40.78	**0.001**
HDL level, mg/dL	39.06±10.76	41.81±8.34	0.061
LDL level, mg/dL	84.75±37.87	87.79±32.71	0.567
Total cholesterol/HDL ratio	4.08±1.36	3.65±0.94	0.019
LDL/HDL ratio	2.23±0.89	2.17±0.87	0.646
Non-HDL cholesterol, mg/dL	112.52±44.59	106.89±32.99	0.348
Lipoprotein (a), mg/dL	35.74±25.86	34.05±22.37	0.642
Apolipoprotein A1, mg/dL	1.31±0.34	1.36±0.28	0.262
Apolipoprotein B, mg/dL	0.94±0.65	0.97±0.71	0.757
Homocysteine, µmol/L	11.41±6.74	11.17±8.08	0.445
hs-CRP level, mg/L	2.18±2.80	1.95±2.20	0.666
FSH IU/mL	10.50±15.99	20.98±29.21	0.001
LH, IU/mL	7.90±12.99	13.17±17.18	<0.0001
Prolactin, ng/mL	30.24±29.69	26.96±32.13	0.005

CAD: coronary artery disease; BMI: body mass index; CPK-MB: creatine phosphokinase myocardial band; HDL: high density lipoprotein; LDL: low density lipoprotein; hs-CRP: high-sensitive C-reactive protein; FSH: follicular stimulating hormone; LH: luteinizing hormone

Table 4: Levels of FSH, LH and prolactin in patients based on parity status.

Number of Parity	No of patients	FSH levels (IU/mL)	LH levels (IU/mL)	Prolactin levels (ng/mL)
0	4	6.43±23.83	4.22±13.88	29.1±18.85
1	1	2.43	10.68	13.62
2	28	13.83±23.23	8.95±15.50	20.48±21.43
3	17	17.6±24.57	8.1±15.15	21.51±20.46
4	7	19.72±22.1	16.84±15.4	9.24±15.78
5	4	19.24±23.6	12.41±16.1	17.78±18.95

FSH: follicular stimulating hormone; LH: luteinizing hormone

The individual parameters of lipid profile increased total cholesterol, triglycerides and LDL and decreased HDL were correlated with patients having increased and normal FSH levels on 3rd day of menstrual cycle. We found that the difference in prevalence of LDL between the two groups was statistically significant (p=0.02). However, for HDL and triglycerides the difference was not statistically significant (p value 0.80 and 0.57, respectively).

DISCUSSION

The present study was performed to evaluate the clinical profile of premenopausal female ≤45 years presenting with chest pain likely to be of cardiac origin, to analyse the risk factors, to define the association of conventional coronary risk factors in the angiographically proven cases of significant coronary artery disease and to assess response to early intervention.

In our study, the mean age was 39±4.9 years which was in line with the study by Waters et al.[6] In the study by Gurevitz et al, the mean age was 45±4.1 years and the 77% patients were premenopausal.[7] Furthermore, significant CAD was found in 63% patients in our study. The study by Waters et al, reported 44% significant CAD, Proudfit et al, reported 24%, and Gurevitz et al, reported 58%.[1,7,8] The difference in results may be due to difference in selection methods for coronary angiography or more likely to be due to increase in incidence and improvement in our understanding of CAD in young females in last 2-3 decades. In present study, most of the patients with significant CAD had single vessel disease and left anterior descending coronary artery was the most involved artery.

Though the history of spontaneous abortions was more frequent in patients with significant CAD, the difference was not statistically significant in our study (p=0.0752). In a meta-analysis by Oliver-Williams et al, a history of miscarriage or recurrent miscarriage was found to be associated with a greater risk of subsequent coronary heart disease.[9] Furthermore, increased hs-CRP was also found to be more prevalent in patients with significant CAD (p=0.015). Gupta et al, demonstrated that in Indian patients presenting with acute coronary syndrome (ACS), hs-CRP level has a correlation with the type of acute coronary syndrome and angiographic severity of CAD.[10]

In premenopausal women undergoing coronary angiography for suspected myocardial ischemia, disruption of ovulatory cycle characterized by hypoestrogenemia seems to be associated with CAD. Earlier reports in primates have suggested that premenopausal atherosclerosis is related to stress-induced central disruption of ovulatory cycling and resulting hypoestrogenemia. These results support the concept that female protection is lost when ovarian function is disrupted. Menstrual irregularity is a predictive of future diabetes and may be a marker for polycystic ovary syndrome. Our finding of a diabetes-related estrogen deficiency, if validated in prospective study, may provide an explanation for the relatively greater coronary risk that diabetes conveys for women than men, which has been observed repeatedly in previous studies but remains unexplained. Our multivariate analyses suggest that hypothalamic hypoestrogenemia is a significant predictor of CAD, consistent with a previous report demonstrating an inverse relationship between estrogen levels and coronary artery severity in premenopausal women and with numerous animal studies implicating estrogen as a key player in atherosclerosis.[11] The use of hormone replacement therapy with conjugated equine estrogen - medroxyprogesterone acetate in older postmenopausal women remains of uncertain value. Thus, simple replacement of estrogen may not fully address the underlying hormonal abnormalities that are associated with hypoestrogenemia of hypothalamic origin. These results are also consistent with previous primate work demonstrating that atherosclerosis is significantly accelerated in monkeys with hypoestrogenemia secondary to disrupted ovarian function, as well as with work in humans demonstrating elevated CAD risk associated with premature menopause in women.

Previous animal and human studies have demonstrated that hypoestrogenemia in females is accompanied by coronary artery dysfunction, characterized by a diminution of normal vasodilation and even vasoconstriction in response to a stressor. Our current results document that premenopausal women with CAD may have hypoestrogenemia and, therefore, may have more adverse coronary arterial dysfunction. Prolactin is increasingly recognized to play a stimulatory role in the inflammatory response. Inflammation is considered of crucial importance in the development of atherosclerosis. Studies involving a small number of subjects suggest that in the acute phase of coronary disease, ischemic strokes, and transient ischemic attacks, plasma prolactin levels are elevated. Although this increase of systemic prolactin may be representative of the general neuroendocrine stress response, a role of prolactin as causal factor in these thrombotic diseases is possible. Furthermore, prolactin may play a role in accelerated arteriosclerosis in early menopause by increasing central as well as peripheral blood pressure and arterial stiffness. In-vitro studies stated that prolactin stimulates integrin-mediated adhesion of circulating mononuclear cells to endothelium and induces vascular smooth muscle cell proliferation. Prolactin may contribute to a higher cardiovascular risk profile and may influence various components within the atherosclerotic lesion. The high level of prolactin receptors within the atherosclerotic plaques suggests that prolactin might be able to modulate the atherosclerotic process.[12-14]

Study limitations

Despite of effective results reported by the present study, it is not devoid of limitations. The main limitation of this study is its design that is non-randomized, single-centred experience with very small sample size. Another limitation is lack of comparison arm Furthermore, to prove these

results further larger studies are required to validate these findings on heterogeneous population.

CONCLUSION

This study concluded that premenopausal females (<45 years) represent a special subgroup of patients where non-conventional risk factors play an important role in the occurrence of CAD. Thus, careful history taking with detailed menstrual and obstetric history (unexplained spontaneous abortion, complications of pregnancy, pre-eclampsia, hormonal irregularities) should be considered in premenopausal women in prevent complexity of disease.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Shinde AS, Shukla AN, Dixit PM. Evaluation of coronary artery risk factors in premenopausal women (<45 years): a single-center prospective study. Int J Res Med Sci 2021;9:1929-34.