

## Evaluation of the Cardiovascular Risk in Women With PCOS

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### Abstract:

**Background:** Evaluation of the cardiovascular (CV) risk in a sample of CV asymptomatic infertile women with polycystic ovary syndrome (PCOS). **Methods:** 100 infertile PCOS women older than 30 years (PCOS group) and 50 fertile non-PCOS women (Non-PCOS group) underwent gynecological and laboratory diagnosis. The diagnostic protocol included determination of body mass index (BMI), Homeostasis model assessment of insulin resistance (HOMA-IR) scoring and cardiologic evaluation using echocardiography, estimation of carotid artery intima-media thickness (CIMT), coronary artery calcium (CAC) score using multi slice non-contrast cardiac CT and cardiac risk ratio (CRR). Study outcomes included the incidence of abnormal cardiac risk parameters and determination of the best minimally invasive modality to be used as screening test. **Results:** The median values of CRR, CIMT and CAC Agatston score were significantly higher among PCOS women than in Non-PCOS women. Estimated cardiac risk parameters were positively correlated with the level of hyperandrogenemia, BMI, and HOMA-IR score. High CRR was found to be the most important predictor for the risk of atherosclerosis as judged by CIMT and CIMT was the most important predictor for the risk of coronary atherosclerosis as judged by CAC score. Statistical analyses defined high BMI and CIMT as the sensitive significant predictors for high CAC score. **Conclusion:** Adult cardiac asymptomatic PCOS women had high cardiovascular risk. Estimation of CRR is non-invasive, cheap and available screening tool and had predictive ability to detect women had high CIMT. CIMT is a minimally invasive predictor for the extent CAC.

**Keywords:** Cardiovascular risk, Polycystic Ovary Syndrome, Infertility, Cardiac risk ratio, Carotid intima-media thickness.

### Introduction

Polycystic ovary syndrome (PCOS) is a widespread endocrine and metabolic disorder which affects both adult and adulthood women (1) and is associated with menstrual irregularity, hyper-

androgenism, and infertility among women of childbearing period (2). PCOS in adolescents is associated with adiposity, higher androgen concentrations and greater menstrual irregularity, in youth PCOS is considered a risk factor for type 2

diabetes mellitus in adulthood (3) and confers an increased risk of cardiometabolic disease in later life (4).

Early identification and treatment of cardiovascular disease risk factors through screening of apparently healthy individuals is crucial for the primary prevention of cardiac insults (5). Carotid intima-media thickness (CIMT), plaque quantification and coronary artery calcium (CAC) scoring have an important role in preventative cardiology to improve cardiovascular risk prediction especially for asymptomatic individuals classified as low-to-intermediate risk (6).

The CIMT is a feature of vascular endothelial inflammatory response leading to gradual trans-differentiation of endothelial cells to adopt the phenotypic characteristics of mesenchymal cells (7). Thickening of intima-media appears in a long subclinical period of atherosclerosis and IMT was found to correlate with atherosclerotic deterioration of the arterial wall in other vascular territories and with cardiovascular events (8). The IMT was defined as wall thickness of  $>0.9$  mm, while focal thickening of  $\geq 1.5$  mm that protrudes into the lumen as asymptomatic carotid plaque increases the risk of cardiac events from 16 to 36% in cardiac asymptomatic patients (9).

The coronary artery calcium (CAC) score is powerful discriminator of cardiovascular risk (10) and was measured using a 16-channel computed tomographic system and reported as an Agatston score, to provide a snapshot of atherosclerotic burden (11). CAC score =0 has a very low future event rate, while non-zero CAC scores are associated with a progressive, graded increase in risk with increased CAC score (12). Moreover, CAC=0 was indicator of a favorable long-term

prognosis of adults aged  $\leq 55$  years, particularly among nonsmokers (10).

### **Objectives**

The present study aimed to evaluate the cardiovascular (CV) risk in a sample of CV asymptomatic infertile PCOS women who are aged  $>30$  years old.

Design:

Prospective observational comparative study

Setting:

Departments of Cardiology, and Internal Medicine, Faculty of Medicine, Tanta and Benha Universities

Ethical consideration

The study protocol was approved by the Local Ethical Committee, Faculty of Medicine, Tanta University (Approval code: 35179/1/22) and was registered at ClinicalTrials.gov. by number NCT05344547.

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### **Patients & Methods**

Women attending the infertility clinics at Tanta and Benha University Hospitals from Feb 2022 till Sep 2022 were eligible for evaluation for the PCOS as a cause of infertility. Gynecological evaluation entails data concerning present and past history of menstrual regularity, previous pregnancy for married women, previous investigations or therapies for PCOS or infertility. PCOS was diagnosed depending on the presence of at least two of the Rotterdam criteria (13, 14). Then, PCOS women fulfilling the inclusion criteria were referred for the concerned outpatient clinics for evaluation of the study parameters which include the following items:

1. Body mass index (BMI): was calculated and graded according to WHO guidelines (15, 16).

2. Insulin resistance (IR) was evaluated using the homeostasis model assessment of IR (HOMA-IR) score with a score of  $>2$  is considered abnormal (17).
3. Cardiac evaluation
  - History taking history of previous acute cardiac attack, hypertension, and manifestations of heart failure, chronic kidney disease, or maintenance of antihypertensive therapy must be inquired about.
  - Clinical examination for the presence of any manifestation of congenital cardiac lesion, valve disease, vascular anomalies or diseases. Then, patients underwent complete cardiologic workup for evaluation of CV risk using the following investigations and scores:
    - a. Doppler echocardiography was performed as previously (18) using an ultrasound system with image analysis by EchoPAC software (General Electric). The following parameters were estimated: left ventricular end diastolic (LVDd) and systolic (LVSD) diameters, the percentage of fractional shortening (FS%), left ventricular mass index, left atrial diameter (LAD), ejection fraction, deceleration time (DcT)
    - b. Carotid IMT was measured as previously described (19), using a longitudinal 2D B-mode image.
    - c. Coronary Artery Calcium (CAC) Score: CAC is quantified through multi slice non-contrast cardiac CT as previously described (20). Calcified coronaries were defined (21) and the CAC Agatston score was calculated (22).

- d. Cardiac risk ratio (CRR) was calculated according to Genest et al. (23) as serum total cholesterol (TC) level divided by serum high-density lipoprotein-cholesterol (HDL-c) level and woman with CRR at  $\geq 3.5$  was considered at risk of cardiac disease (24).

#### **Exclusion criteria**

Age younger than 30 years old, BMI  $>35$  kg/m<sup>2</sup>, presence of acute or chronic inflammatory diseases, diabetes mellitus, hyperprolactinemia, thyroid dysfunction, Cushing's syndrome, congenital adrenal hyperplasia, adrenal tumor or ovarian tumor, autoimmune disease, malignancy, central nervous system disease, current or previous use of oral contraceptives within 6 months of enrollment were excluded from the study. Patients had congenital cardiac lesions, manifestations of hypertension especially unequal carotid pulse, neurological affection, renal diseases or family history of cardiac or cerebrovascular insults, ejection fraction  $<50\%$ , regional wall motion abnormalities and significant valvular diseases were excluded.

#### **Inclusion criteria and grouping**

Infertile PCOS women older than 30 years and free of exclusion criteria were enrolled in the study as PCOS group. Fifty non-PCOS women of age- and BMI cross-matched to the enrolled PCOS women with regular menstrual cycles or fertile if married were collected as control (non-PCOS) group. Only women who signed the written informed consent will be enrolled in the study.

#### **Laboratory investigations**

##### **Blood Sampling**

All enrolled women were asked to attend the hospital lab fasting for 12 hours and gave blood sample for estimation of blood

lipid profile and to re-attend on the 2<sup>nd</sup> day fasting for 8 hours to give another sample for estimation of fasting blood glucose and determination of hormonal profile levels. Blood samples were obtained under complete aseptic condition for estimation of blood glucose levels and serum levels of hormones and lipids.

Estimated parameters

1. Blood glucose levels were estimated by glucose oxidase method using BT1500 Automatic biochemistry analyzer (SPAN Diagnostics, Gujarat India).
2. Serum levels of total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were estimated by photoluminescence methods using BT1500 Automatic biochemistry analyzer (SPAN Diagnostics, Gujarat India).
3. Serum levels of insulin, testosterone (T) and dehydroepiandrosterone sulfate (DHEA-S) using Automatic Immunoassay Analyzer (MAGLUMI 600, Snibe Diagnostic Co., Ltd., China).

Study outcomes

1. The primary outcome is the incidence of abnormal cardiac risk parameters among PCOS women who were apparently cardiac free women.
2. The secondary outcome is the best minimally invasive diagnostic approach to be used as screening test for these women.

Sample size calculation

Sample size calculation was based percent of difference in proportion of CAC>10 between PCOS and control groups as documented previously (25). Using G power calculator to calculate difference between 2 proportions using exact test

with expected difference of 23.3%, 2-tailed, with  $\alpha$  error =0.05 and power of 80%. The minimal calculated sample size was 84 PCOS women and 42 non-PCOS women as control group, and so as to get higher power, 100 PCOS women and 42 Non-PCOS women were recruited for the current study.

**Statistical analysis**

The results were analyzed using One-way ANOVA and Chi-square ( $X^2$  test) test and the relation between the studied variate was studied using the Spearman's correlation analysis. The predictability of the studied variate for outcomes was evaluated using the Receiver Characteristic Curve and the Automatic Linear Modeling analyses using the IBM® SPSS® Statistics (Version 22, 2015; Armonk, USA). Significance of the results was determined at cutoff point of  $P < 0.05$ .

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## Results

The study included 135 infertile PCOS women, 35 were excluded for not fulfilling the inclusion criteria and 100 women were enrolled in the study (Fig. 1).

There were 37 single and 63 married women and all were older than 30 years and had BMI<35 kg/m<sup>2</sup> with non-significant differences between PCOS and Non-PCOS women. All married control women were fertile, while among PCOS women, 53 women had primary and 10 had secondary infertility. All single control women had regular menstrual cycle free of abnormalities regarding duration or amount of bleeding, while 26 PCOS single women had oligomenorrhea and 11 had amenorrhea. Seventy-five women; 4 Non-PCOS and 71 PCOS women had ovarian volume >10 cm<sup>3</sup> with significantly higher frequency among the PCOS women

with significantly median value of ovarian volume in comparison to Non-PCOS women (Table 1).

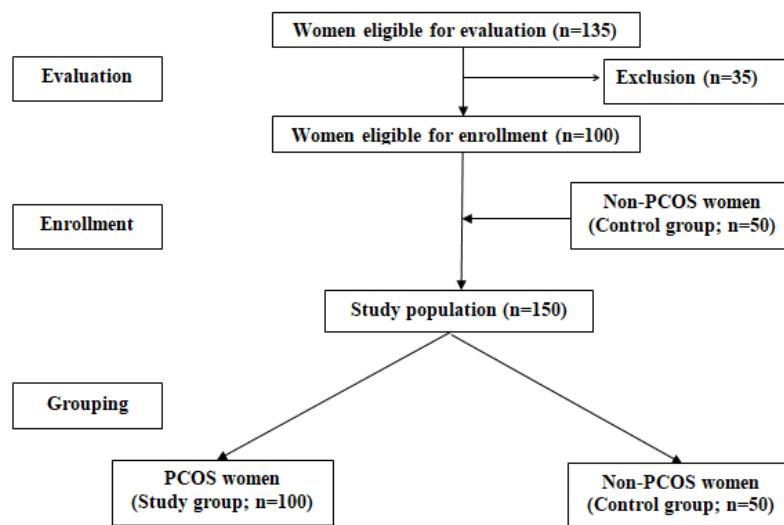


Fig. (1): Study Flow Chart

Table (1): Demographic and clinical data of study participants

Data	Group	Non-PCOS (n=50)	PCOS (n=100)	P value
Age (year)	30-35	27 (54%)	52 (52%)	0.418
	36-40	18 (36%)	24 (24%)	
	>40	5 (10%)	14 (14%)	
	Mean (±SD)	35.8 (±2.9)	36 (±3.3)	0.718
BMI (kg/m <sup>2</sup> )	Overweight (25-29.9)	6 (12%)	10 (10%)	0.708
	Obese (30-34.9)	44 (88%)	90 (90%)	
	Mean (±SD)	32.1 (±1.5)	32.3 (±1.3)	
Marital status	Married	29 (58%)	63 (63%)	0.553
	Single	21 (42%)	37 (37%)	
Fertility status of married women	Fertile	29 (100%)	0 (0%)	-
	Primary infertility	0	53 (77.9%)	
	Secondary infertility	0	10 (22.1%)	
Menstrual status of single women	Regular	21 (100%)	0 (0%)	-
	Oligomenorrhea	0	26 (70.3%)	
	Amenorrhea	0	11 (29.7%)	
Ovarian volume (mm <sup>3</sup> )	<10	46 (92%)	29 (29%)	<0.001
	>10	4 (8%)	71 (71%)	
	Median volume [IQR]	6.75 [6.25-7.9]	10.95 [9.5-12.7]	<0.001
HOMA-IR score	Insulin resistant	5 (10%)	31 (31%)	<0.001
	Insulin sensitive	45 (90%)	69 (69%)	
	Median score [IQR]	0.42 [0.31-0.53]	1.4 [1.12-2.15]	

According to the calculated HOMA-IR score, 31 PCOS and 5 Non-PCOS were IR with significant difference regarding the frequency and median score. Seventy-two PCOS women were hyperandrogenemic with significant difference between both groups as regards the frequency and serum

levels. Serum DHES, TC and TG levels were significantly higher, while serum HDL-c levels were significantly lower in PCOS than Non-PCOS women (Table 2). All Non-PCOS and 10 PCOS women had CRR of <3.5 with significantly lower frequency of women had CRR of <3.5 and

significantly higher median value among PCOS. The median value of estimated CIMT was significantly higher in PCOS women. Sixty seven women had CAC score of 0, 38 women had CAC score of <10 and 45 women had CAC score of >10 with significantly ( $p=0.008$ ) higher

distribution of PCOS women among higher CAC Agatston scores. Both calculated mean and median CAC Agatston score values were significantly ( $0.0005$  &  $0.0009$ , respectively) higher in PCOS women (Table 3)

**Table (2):** Laboratory data of the study participants

Data	Group	Non-PCOS (n=50)	PCOS (n=100)	P-value
<b>HOMA-IR index</b>	<b>Insulin sensitivity</b>	5 (10%)	31 (31%)	0.005
	<b>Insulin resistant</b>	45 (90%)	69 (69%)	
	<b>Insulin sensitive</b>	0.42 [0.31-0.53]	1.4 [1.12-2.15]	<0.001
<b>Serum testosterone</b>	<b>Frequency of hyperandrogenemia</b>	0	72 (72%)	<0.001
	<b>Mean (<math>\pm</math>SD) level</b>	0.388 $\pm$ 0.09	0.996 $\pm$ 0.2	<0.001
<b>Serum Dehydroepiandrosterone sulfate</b>		14.8 $\pm$ 2	24.1 $\pm$ 5.1	<0.001
<b>Total cholesterol (mg/dl)</b>		160.9 $\pm$ 9.6	183.7 $\pm$ 17.7	<0.001
<b>High-density lipoprotein cholesterol (mg/dl)</b>		49.2 $\pm$ 2.5	39.3 $\pm$ 3.6	<0.001
<b>Triglycerides (mg/dl)</b>		51 $\pm$ 8	82.9 $\pm$ 11.3	<0.001
<b>Low-density lipoprotein cholesterol (mg/dl)</b>		60.7 $\pm$ 6	61.5 $\pm$ 14.9	0.351

**Table (3):** Cardiac risk data of the study participants

Data	Group	Non-PCOS (n=50)	PCOS (n=100)	P-value	
<b>CRR (TC/HDL)</b>	<b>Frequency</b>	<3.5	50 (100%)	10 (10%)	<0.001
		$\geq 3.5$	0	90 (90%)*	
	<b>Median [IQR]</b>		3.33 [3.1775-3.39]	4.68 [4.35-5.2]*	<0.001
<b>CIMT (mm)</b>	<b>Median [IQR]</b>		0.44 [0.38-0.48]	0.485 [0.45-0.55]*	<0.001
	<b>Distribution of CAC</b>	<b>0</b>	30 (60%)	37 (37%)	0.008
<b>CAC score</b>		<b>&lt;10</b>	12 (24%)	26 (26%)	
		<b>10-49</b>	8 (16%)	23 (23%)	
		<b><math>\geq 50</math></b>	0	14 (14%)*	
	<b>Mean (SD)</b>		5.12 $\pm$ 10.2	16.31 $\pm$ 20.8*	0.0005
	<b>Range</b>		0-42	0-69	
	<b>Median [IQR]</b>		0 [0-6]	6.5 [0-26.75]*	0.0009

\* indicates significant difference;  $p>0.05$  indicates non-significant difference

Estimated CIMT and CRR showed positive significant correlation with both ovarian size and serum testosterone levels, while CAC score showed positive significant correlation with serum testosterone levels. Regarding PCOS-metabolic disturbances, CAC score, CIMT and CRR were positively correlated with BMI in decreasing order of significance and both of CAC score and CIMT were positively correlated with HOMA-IR

score. Only, CIMT showed positive significant correlation with age of PCOS women (Table 4).

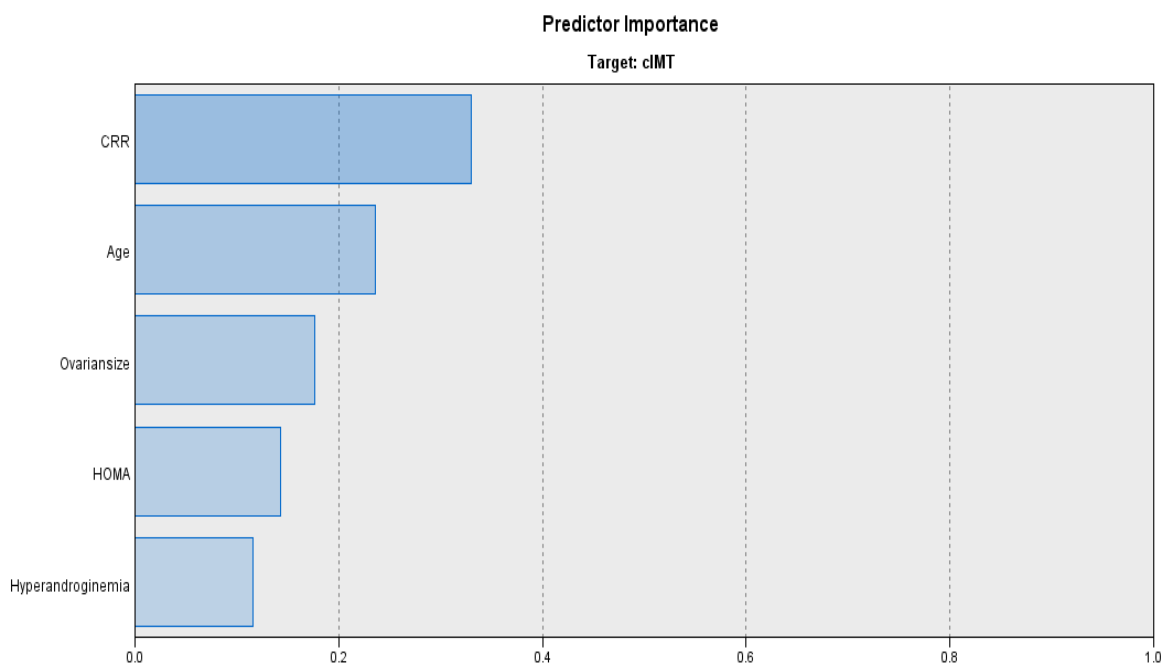
Evaluation of the variables correlated with cardiac risk variables as predictors for the risk of atherosclerosis as judged by CIMT defined high CRR as the most important predictor for CIMT with predictive value of 33%, followed by older patients' age by 24%, ovarian size by 18%, high HOMA-IR score by 14% and hyperandrogenemia

by 12% (Fig. 2). For prediction of coronary atherosclerosis and risk of oncoming cardiac events, high CIMT was

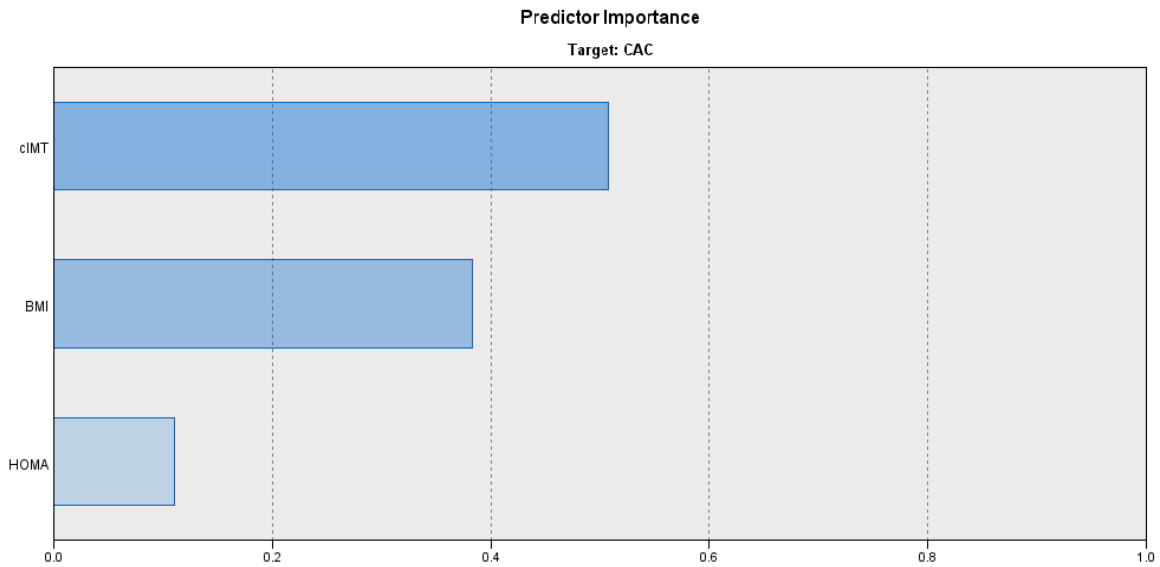
the most important predictor by a value of 51%, followed by high BMI by 38% and high HOMA-IR score by 11% (Fig. 3).

**Table (4):** Spearman's correlation analysis between cardiac risk variables and PCOS-related endocrinal and metabolic disturbances in the studied PCOS women

Variables	CAC score		cITM		CRR	
	Rho.	P	Rho.	P	Rho.	P
Age	0.151	0.135	0.224	0.025	0.072	0.477
BMI	0.349	<0.001	0.265	0.008	0.219	0.029
Ovarian size	0.063	0.534	0.362	<0.001	0.287	0.004
Hyperandrogenemia	0.257	0.010	0.375	<0.001	0.362	<0.001
HOMA-IR score	0.224	0.025	0.241	0.016	0.122	0.225
CIMT	0.412	<0.001	-	-	0.263	0.008
CRR	0.263	0.008	0.361	<0.001	-	-



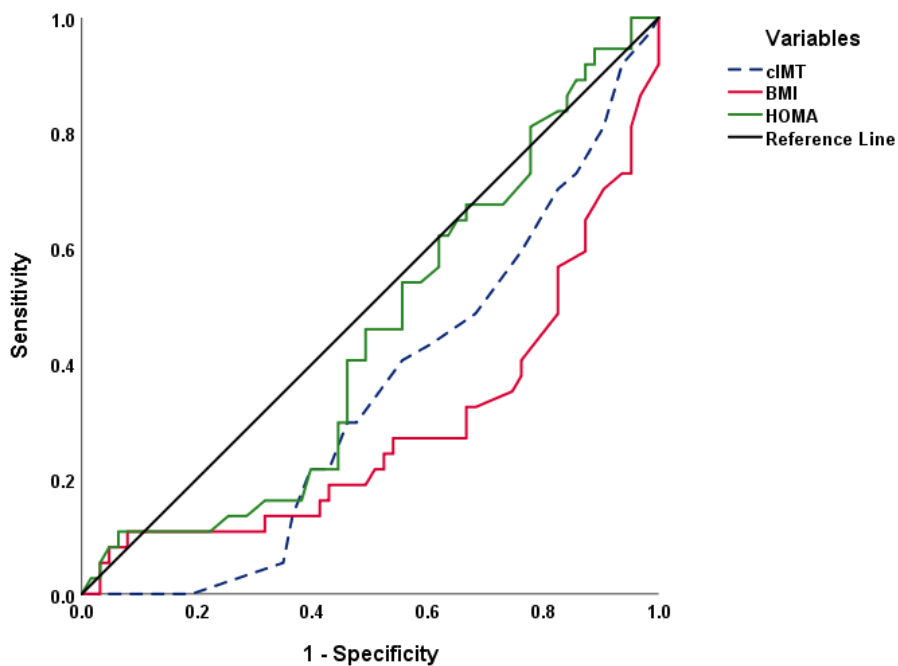
**Fig. (2):** Importance of variables correlated with cardiac risk markers as predictors for high CIMT



**Fig. (3):** Importance of variables correlated with cardiac risk markers as predictors for high CAC score

ROC curve analysis using multivariate analysis for BMI, CIMT and HOMA-IR as sensitive predictors for high CAC score as judged by the significance of the area under the curve (AUC) compared to the area under the reference line defined high BMI as the most significant predictor with AUC of 0.287 ( $\pm 0.056$ ; 95% CI: 0.177-

0.397) and P-value  $< 0.001$ , followed by high CIMT with AUC of 0.347 ( $\pm 0.054$ ; 95% CI: 0.241-0.454) and P-value of 0.011; while HOMA-IR score was non-significant predictor with AUC of 0.448 ( $\pm 0.059$ ; 95% CI: 0.333-0.563) and P-value of 0.128 as shown in figure 4.



**Fig. (4):** ROC curve analysis of the most important predictors for high CAC score as determined by the Automatic Linear Modeling analysis

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## Discussion



The current study detected significant differences between cardiac asymptomatic adult PCOS women older than thirties and their age-matched control fertile women as regards cardiac risk ratio (CRR), the carotid intima-media thickness (CIMT) and the coronary artery calcification (CAC) score. These findings point to the fact that these women, despite being apparently healthy and cardiac asymptomatic are at risk of development of cardiovascular diseases (CVD) or cerebral insults.

Similarly, one study reported a Hazard ratio (HR) of 1.7 for CVD development in PCOS Denmark women with a total event rate of CVD of 22.6 versus 13.2/1000 women/year in controls and PCOS women were significantly younger at time of CVD diagnosis than controls (26). Another study also found the overall incidence of coronary artery disease (CAD) was 63% higher in PCOS women than in controls (27). Thereafter, a literature review found PCOS women had increased risks of hypertension and non-fatal cerebrovascular disease events compared to women without PCOS (28) and one comparative study reported that normotensive non-obese PCOS women were prone to have higher left ventricular mass index than healthy controls and it was positively correlated with insulin resistance (29).

Further, two recent studies documented that PCOS women are more likely to develop hypertension from early adulthood, independent of BMI (30, 31). Moreover, it was reported that the crude rates of the myocardial infarction, stroke, angina, revascularization, and cardiovascular mortality were higher in PCOS women than control women (32).

The detected significantly higher CRR and HOMA-IR score for PCOS women goes in hand with a previous study that detected a prevalence of IR was 39.6 to 55%, glucose intolerance rate was 7.2-28.1% and that of dyslipidemia was 54.1- 70.4% among PCOS women in different Brazilian regions (33). Further, significant correlations were reported between CRR and HOMA-IR score and with CIMT and CAC score. Thus, the detected high cardiac risk as judged by the estimated CIMT and CAC could be attributed to the PCOS-associated metabolic disturbance in diabetogenic direction, and the detected positive correlation between cardiac risk markers and BMI may be the underlying mechanism for the reported high cardiac risk.

These findings are coincident with the previously detected increased incidence of CAD by 20-fold greater in PCOS women with cardiometabolic comorbidities than those free of these comorbidities (27). Further, it was found that the genetic risk of obesity and metabolic effects are the common denominator of both PCOS and CAD risk (34). Also, it was detected that PCOS-induced hypertension is aggravated by obesity (30) and PCOS-associated obesity and hyperandrogenemia may explain the association between PCOS and cardiometabolic diseases (35).

Statistical analyses defined high CRR and HOMA-IR score and severity of hyperandrogenemia as the important predictor of high CIMT, while high CIMT, BMI and HOMA-IR could predict CAC score. Thus, the severity of metabolic disturbances in association with obesity is the most important predictors for CV insults.

In line with these findings, the results of a previous study suggested that obesity not hyperandrogenemia negatively related to early development CV risk markers in PCOS women (36). Another study indicated increased CV risk and found the diagnostic features of PCOS are the strongest predictor of CIMT (37). Then, CV parameters in PCOS women were independently associated with BMI with significantly higher CIMT measures in women with BMI levels  $\geq 25$  kg/m<sup>2</sup> than in women had BMI levels  $< 25$  kg/m<sup>2</sup> (38). In support of the role of obesity as a coronary risk factor, one study detected significantly higher prevalence of CAC in obese than in non-obese (39) and CAC score of 1-99 AU can predict high-risk plaque (40). Moreover, it was found that bariatric surgery for severe obesity significantly reduces the future risk of developing CV comorbidities with significant reduction in CAC scores (41).

## Conclusion

Adult cardiac asymptomatic PCOS women older than thirties had high cardiovascular risk. Estimation of coronary risk ratio is non-invasive, cheap and available screening tool and had predictive ability for detection of women had high CIMT. CIMT is a minimally invasive diagnostic modality that can predict the extent of coronary artery calcification.

## Recommendation

PCOS women older than thirties must be considered as cardiac risky patients even if they were asymptomatic and so evaluation of atherosclerotic status of these women using estimation of CRR and CIMT must be a part of routine evaluation.

## Limitations

No intervention was undertaken to reduce the predisposing factors for such high cardiac risk.

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