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ASSESSMENT OF CARDIOVASCULAR RISK IN WOMEN WITH PCOS: A NARRATIVE REVIEW

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ABSTRACT Polycystic ovarian syndrome (PCOS) is one of the commonest endocrinopathy of women of reproductive age globally. This clinical condition not only dysregulates the reproductive axis, but also a risk factor for hyperinsulinemia, insulin resistance, dyslipidaemia, T2DM. All these metabolic states aggravate the cardiovascular risk in women with PCOS. The aim of this review is to provide an overview of evidences of subclinical cardiovascular risk in PCOS women and synthesize the result. To attain this aim, the published research articles were reviewed using the databases PubMed, Google scholar and EMBASE employing key words PCOS, cardiovascular risk, arterial stiffness, endothelial function to obtain relevant information. Total 162 articles were searched and after applying eligibility criteria, 12 articles have been included for qualitative synthesis of the information. Most of the studies are cross-sectional, case-control study conducted on pre-, peri and menopausal, obese, lean women with PCOS. The study participants were mostly diagnosed on the basis of Rotterdam criteria. But, other criteria such as National Institutes of Health criteria (NIH), Androgen Excess Society criteria (AES) were also used to diagnose the condition. Mostly these studies recorded arterial stiffness as assessed by pulse wave velocity (PWV), augmentation index (AIx) and endothelial dysfunction as assessed by brachial artery flow mediated vasodilatation (FMD). The findings of few cardinal systematic review and meta-analysis were also reported. These studies mainly analysed the data obtained for subclinical cardiovascular status of women with PCOS as assessed by carotid intima media thickness (cIMT), carotid artery calcium (CAC) score and FMD. Majority of the studies concluded that women with PCOS display enhanced arterial stiffness and endothelial dysfunction in comparison to age and BMI-matched healthy control group, though controversy exists is the literature. In this regard, the existing traditional cardiovascular risk factors in PCOS women, make them more prone to cardiovascular disease. It needs further prospective study with hard cardiovascular outcome to prove this point undoubtedly. It must be emphasized that regular cardiovascular screening might be advocated for this vulnerable population to prevent any major cardiovascular eventuality.

KEYWORDS : PCOS (Polycystic ovary syndrome), cardiovascular risk, arterial stiffness, endothelial dysfunction

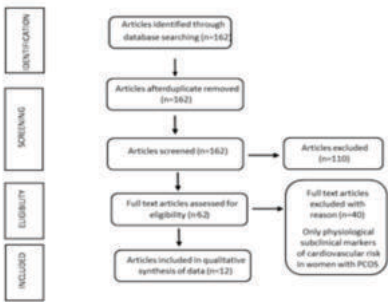
INTRODUCTION

Polycystic ovarian syndrome (PCOS) is one of the commonest endocrinopathy affecting 4-21% of women of reproductive age globally (Osibogun et al., 2020). The diagnosis of PCOS mainly depends on Rotterdam criteria, which includes oligo anovulation, hyperandrogenism and polycystic ovaries (≥ 12 follicles measuring 2-9 mm in diameter and/or ovarian volume 10 mL in at least one ovary)(Rotterdam ESHRE/ASRM, 2004). The characteristic clinical symptoms include oligo or amenorrhoea, acne, hirsutism, infertility and mood disorders. However, the condition not only dysregulates the reproductive axis, but also a risk factor for hyperinsulinemia, insulin resistance, dyslipidaemia, Type 2 diabetes mellitus (T2DM). Moreover, there is a significant difference in phenotypic presentation of this disorder. There are four different phenotypes such as phenotype-A [HA (hyperandrogenism, clinical or biochemical) + OD (ovarian dysfunction) + PCO (polycystic ovary)], phenotype-B (HA+OD), phenotype-C [HA+PCOM (polycystic ovary morphology)] and phenotype-D (OD+PCOM). Out of these, women with phenotype-A more commonly seek for medical advice. They are more obese, hyperandrogenic and present with more severity. Phenotype-C is more common in general population (Mumuslglu and Yildiz et al., 2020). Recently, international evidence-based guideline for the assessment and management of PCOS has refined Rotterdam criteria in adolescence age group to hyperandrogenism and oligo-/anovulation. Furthermore, it has recommended against ultrasound due to poor specificity of polycystic ovaries in this age group (Teede et al., 2018). There is also National Institute of Health (NIH) criteria for diagnosing PCOS which includes presence of clinical and/or biochemical hyperandrogenism and oligo/amenorrhoea anovulation (Zawadski and Dunaif, 1992). Till date the etiology of this disease is not so clear. But emphasis is on its multi-factorial origin encompassing gene-environment interaction. Therefore, life style may play an important role in its pathogenicity. There are ample evidences that PCOS is associated with metabolic syndrome (MetS) which comprises of insulin resistance, hyperinsulinemia, dyslipidemia, dysglycemia and accelerated atherosclerosis. All these metabolic states enhance the cardiovascular risk in a given individual, more so in PCOS women because of two remarkable hormonal disturbances namely insulin resistance and hyperandrogenemia (Gillbert et al., 2018). The aim of this review is to provide an overview of evidences of subclinical cardiovascular risk in PCOS women and synthesize the result.

Methods

The published research articles were reviewed using the databases PubMed, Google scholar and EMBASE. The search terms were "PCOS", "cardiovascular risk", "arterial stiffness" and "endothelial function". Total 162 articles have been found, inclusive of observational studies, systematic and narrative reviews. The articles which were published in English from 2002 to 2022 were included. 12 articles which provided the evidences of assessment of subclinical cardiovascular risk markers in women with PCOS of both phenotypes (obese and lean) were discussed in the present narrative review. The flow chart for inclusion of articles is shown in figure 1. The overview of the research articles has been discussed in table 1.

Figure 1. Flow chart showing inclusion of research articles for narrative synthesis of information



PCOS and traditional cardiovascular (CVD) risk factors

Previous studies which attempted to determine the degree of CVD risk in PCOS vs. general population, have demonstrated mixed findings. One meta-analysis has documented that there is a 2-fold risk of arterial disease for women with PCOS in comparison to women without PCOS. BMI adjustment did not affect the finding, which is suggestive of perturbation of functionality of cardiovascular system by the pathogenic mechanism of PCOS (de Groot et al, 2011). However, other study has suggested that absolute risk of CVD conferred by PCOS may be small, given the younger patient population, who have lesser traditional CVD risk (Carmina et al., 2018). More importantly, CVD risk is not uniform across PCOS patients. It is of interest to discuss

about the traditional cardiovascular risk factors in PCOS women as reported by previous studies.

Obesity

It was reported that 60% of PCOS women are obese (Lim et al., 2012). Moreover, obesity has a bidirectional relationship with PCOS condition which means PCOS women may gain weight over time and those who are overweight may predispose to PCOS (Cooney and Dokras, 2021). It is to be noted that white women with PCOS are more obese in comparison to Asians (10.8 fold vs 2.3 fold respectively, P<0.001) (Lim et al., 2012). It was also observed that the risk for obesity and central obesity are similar, but it is higher in HA phenotypes (40% vs 11%, P<0.001) (Daan et al., 2014).

Impaired glucose tolerance (IGT) and T2DM

A meta-analyses of 40 studies reported that women with PCOS have increased risk of IGT and T2DM (OR: 3.26, OR: 2.87) (Kakoly et al., 2018). Women with PCOS of Asian origin has highest risk of IGT (5.2 fold). Two longitudinal studies carried out for 10 years documented higher incidence of DM in PCOS as compared with control with adjustment for BMI (Rubin et al., 2017; Kakoly et al., 2019). Therefore, it may be inferred that pre-menopausal, peri-menopausal and menopausal women with PCOS are at increased risk of IGT and DM.

Dyslipidaemia

One meta-analyses of 30 studies has documented that higher mean serum level of LDL-c, TG and lower HDL-c in women with PCOS in comparison to women without PCOS, though the effect size was small. Even the same result persisted in BMI-matched study (Wild et al., 2011). Furthermore, a cross-sectional, multi centric study analysed 2288 well phenotyped women with PCOS of 18-45 years of age group. The study reported that HA phenotype was associated with a higher risk of dyslipidaemia even after correction for age, smoking, BMI, center and ethnic origin (Daan et al., 2014). Dyslipidaemia is also evident in older women (>40 years of age) with PCOS (Cooney and Dokras, 2020).

Hypertension (HTN)

It was reported that overall pooled prevalence of HTN was higher in women with PCOS compared with controls (15% vs 9%, respectively). Moreover, a higher prevalence of HTN in HA phenotype of PCOS has been documented. But this association is stronger in reproductive aged women with PCOS than menopausal women (Daan et al., 2014).

Metabolic syndrome (MetS)

Metabolic syndrome (MetS) is a conglomeration of metabolic dysregulation, which includes obesity, hyperglycemia/insulin resistance, dyslipidaemia and hypertension. Mean prevalence of MetS in younger adults with PCOS is about 30% and they are at higher risk of development of MetS in comparison to age-matched control (OR 2-3 folds) (Lim et al., 2019). This increased prevalence was also observed in BMI-matched studies, though it was not observed in lean women with PCOS (Behboudi-Gandevani et al., 2018). Asian women with PCOS have a greater risk of development of MetS (OR 3.5 fold). Odds of MetS in women with HA phenotype was found to be more in comparison to women with PCOS without HA phenotype (OR 2.21) (Yang et al., 2016). It is evident from the foregoing discussion that women with PCOS have a greater risk of development of cardiovascular and metabolic morbidity in comparison to age and BMI-matched controls. However, women with PCOS of hyperandrogenic (HA) phenotype are more prone to develop cardiovascular and metabolic morbidity than other phenotypes. Besides these traditional cardiovascular risk factors, subclinical cardiovascular disease (CVD) i.e; arterial stiffness, endothelial dysfunction are also considered to accelerate major cardiovascular events.

PCOS and subclinical cardiovascular disease

Several studies have been conducted to determine subclinical CVD in women with PCOS at the earliest. This knowledge may help to prevent or delay the incident major cardiovascular event. In the present review those studies have been discussed with the major outcomes.

Moreover, there are several surrogate markers for determination of subclinical CVD such as carotid intima media thickness (cIMT), flow mediated vasodilatation (FMD) on brachial artery to ascertain endothelial dysfunction, carotid artery calcium (CAC) score, which is measured with cardiac computerized tomography or magnetic resonance imaging (Cooney and Dokras, 2021). Arterial stiffness can also be determined by pulse wave velocity. Carotid femoral pulse wave velocity is the gold standard for assessment of arterial stiffness. Brachial ankle pulse wave velocity is also used to determine arterial stiffness which corresponds well with carotid femoral pulse wave velocity (Sugawara et al., 2005). Several studies have utilised these various non-invasive surrogate markers of subclinical CVD to ascertain cardiovascular risk in women with PCOS, which has been discussed in the forthcoming section.

A case-control, cross-sectional study was conducted in reproductive aged amenorrheic and eumenorrheic, non-obese women with PCOS as diagnosed by Rotterdam criteria and healthy control (18-30 years) to endothelial function as assessed by brachial artery flow mediated vasodilatation (FMD). Though the baseline brachial artery diameter was similar in all the participants, following reactive hyperemia, greater vasodilatation was observed in controls and eumenorrheic PCO patients than PCOS patients (Battaglia et al., 2008). Another case-control, cross-sectional study conducted on non-obese women with PCOS concluded that FMD of brachial artery was significantly lower in women with PCOS as compared to control, but no significant difference of arterial stiffness markers was observed between groups. This study further inferred that young, non-obese women with PCOS have abnormal endothelial function (Cussons et al., 2009). Ketel et al (2009) conducted a case-control, cross-sectional study on pre-menopausal, obese and lean women with PCOS and age, BMI-matched controls, documented that central obesity in young, obese women with PCOS is associated with increased arterial stiffness. This study further emphasized that focus should be on central fat mass reduction (Ketel et al., 2010).

In another cross-sectional, case-control study, augmentation index (AIx) was found to be significantly higher in pre-menopausal, non-obese PCOS women after adjustment for age. This study further concluded that central arterial stiffness is predominant in non-obese PCOS women (Dessapt-Baradez et al., 2011). However, Sasaki et al (2011) documented that baPWV was significantly higher in women with PCOS, but not aortic augmentation index (Sasaki et al., 2011). Interestingly, Rees et al (2014) documented that no significant difference of aortic PWV between women with PCOS and control group (Rees et al., 2014). A systematic review and meta-analysis summarised that mean cIMT is higher in women with PCOS when compared with non-PCOS women. The estimate of mean difference in cIMT was 0.073 mm (P<0.0001). Furthermore, this study advocated screening for CVD risk factors in women with PCOS to decrease progression of CVD (Meyer et al., 2012). Sprung et al (2013) reported in a systematic review and meta-analysis that pooled mean FMD of PCOS women is 3.4% lower (95% CI 1.9 to 4.9) than control women after adjusting for age and BMI, which is indicative of endothelial dysfunction (Sprung et al., 2013). However, a recent cross-sectional study has refuted the earlier observation. It documented that FMD and cIMT did not differ significantly neither between PCOS patients and control, nor between PCOS phenotypes. Rather, lower FMD was observed in PCOS with MetS specially in hyperandrogenic phenotypes (Krentowska et al., 2021). Interestingly, another systematic review and meta-analysis summarised the result of 104 studies. FMD was reported to be impaired in PCOS women by most of the studies and cIMT was also altered in women with PCOS. But, the same article has admitted that contradictory results exist in the literature (Alexandraki et al., 2021). Gomez et al (2022) has conducted systematic review and meta-analysis of 21 studies and suggested that decrease FMD (3.4%) in reproductive-aged women, which is aggravated in obese PCOS women, specially if they are also suffered from MetS. PWV was also higher in the same group of PCOS patients when compared with age and BMI-matched controls (Gomez et al., 2022). A narrative review of 9 studies reiterated more or less same findings that higher CAC score and cIMT are present in women with PCOS as compared to control even after adjustment for age and BMI. Significantly lower FMD was observed in PCOS women than age-matched control, though conflicting result exists (Guan et al., 2022). It has been argued that this finding may be due to hyperandrogenism in PCOS as higher androgen level was associated with endothelial dysfunction as assessed by FMD in postmenopausal women (Mathews et al., 2019).

Table 1. Studies of subclinical cardiovascular risk markers in women with Polycystic Ovarian syndrome (PCOS)

Sr. no.	First author (Ref no.)	Mean age and BMI	Number of cases and controls	Criteria applied/ Phenotype	No. of articles / Study design	Methods for assessment of vascular health	Outcomes reported/Summary of evidence
1.	Battaglia et al., 2008 (17)	18-30yr/ 20-30 kg/m2	PCOS-28, eumenorrheic PCOS-17, eumenorrheic volunteer - 15	Rotterdam criteria	Case control, cross-sectional	Brachial artery flow mediated vasodilatation (FMD)	After reactive hyperemia, greater vasodilatation observed in controls and eumenorrheic PCO patients in comparison to PCOS
2.	Cussons et al., 2009 (18)	>18 yr/ <30 kg/m2	PCOS-19, Healthy controls-19	Rotterdam criteria	Case control, cross-sectional	Brachial artery flow mediated vasodilatation (FMD), pulse wave velocity (PWV), augmentation index (AI)	FMD of brachial artery was significantly lower in PCOS women compared with control. But no significant difference was observed in markers of arterial stiffness between groups.
3.	Ketel et al., 2010 (19)	Pre-menopausal, <30 kg/m2	Obese PCOS-18 Obese control-13 Lean PCOS-22 Lean control-17	Rotterdam criteria	Case control, cross-sectional	Carotid femoral pulse wave velocity (cfPWV), aortic augmentation index (AIx)	In young, obese women with PCOS, (central) obesity rather than PCOS itself associated with increased arterial stiffness.
4.	Dessapt-Baradez et al., 2011 (20)	Pre-menopausal, <30 kg/m2	PCOS-14 Control-12	Rotterdam criteria	Case-control, cross-sectional	AIx, cfPWV, central (aortic) blood pressure	AIx was significantly higher in PCOS women after adjustment for age.
5.	Sasaki et al., 2011 (21)	Pre-menopausal, <30 kg/m2	PCOS-54 Healthy control-24	Rotterdam	Case-control, cross-sectional	baPWV, AIx	baPWV was significantly higher in women with PCOS than that for control, but not aortic augmentation index
6.	Rees et al., 2014 (22)	16-45 yr, 27-33 kg/m2	PCOS-84 Control-95	Rotterdam	Cross-sectional study	Aortic pulse wave velocity (aPWV)	No significant difference of aPWV was observed bet ween groups after adjustment for age and BMI
7.	Meyer et al., 2012 (23)	22-40 yr, 21-30 kg/m2	PCOS - 1123 control-913	NIH, AES and Rotterdam/all	19 articles/ Systematic review and meta-analysis	cIMT	Higher mean cIMT in women with PCOS compared with non-PCOS women.
8.	Sprung et al., 2013 (24)	PCOS -23-31 yr, BMI-21-29 kg/m2 Control- 23-34 yr, BMI – 21-29 kg/m2	PCOS-441 control-281	Rotterdam	7articles / Systematic review and meta-analysis of observational studies	FMD	Pooled mean FMD of PCOS women 3.4% lower (95% CI 1.9 to 4.9) than control women after adjusting for age and BMI.
9.	Krentowska et al., 2021 (25)	Pre-menopausal	PCOS – 154 Control-113	Rotterdam	Cross-sectional	FMD, cIMT	FMD and cIMT did not differ significantly neither between PCOS patients and control, nor between PCOS phenotypes. PCOS with MetS specially in hyperandrogenic phenotype presented lower FMD.
10.	Alexandraki et al., 2021 (26)	Pre-menopausal	PCOS-11-200 Control-10-148	Rotterdam	104 studies/ Systematic review and meta analysis	FMD, cIMT	FMD was impaired in PCOS women than control. cIMT was also altered in most of included studies. However, contradictory result exists.

11.	Gomez et al., 2022 (27)	Pre-, peri and post-menopausal	PCOS-47-200 Control-35-200	NIH, AES and Rotterdam/all	21 studies/ systematic review	FMD, PWV	FMD 3.4% lower in reproductive-aged women with PCOS. Presence of obesity and MetS in them increases the risk for lower FMD. PWV was increased in reproductive aged women with PCOS.
12.	Guan et al., 2022 (28)	Pre-, peri- and postmenopausal	Pooled number of participants not mentioned	NIH, AES and Rotterdam/all	studies/narrative review	Coronary artery calcium (CAC) score, cIMT, FMD	Greater prevalence of CAC score, cIMT in women with PCOS compared to control, even after adjustment for age and BMI. Significantly lower FMD was observed in women with PCOS compared to age-matched control, though conflicting result exists.

Why there are so conflicting results?

There may be various reasons which may be responsible for the conflicting outcome of the subclinical CVD assessment in women with PCOS. First of all various diagnostic criteria have been applied to diagnose PCOS. Secondly, there is also variable age of women participants. Moreover, hormonal status gets changed in women with aging which can influence the traditional cardiovascular risk factors. This may aggravate the subclinical cardiovascular risk. It is also to be noted that PWV is influenced by aging and systemic blood pressure. Even though, hyperandrogenic phenotype display enhanced arterial stiffness and endothelial dysfunction. The causality of it has to be determined further. Thirdly, among the traditional cardiovascular risk factors, obesity and MetS emerge as one of the determining factors for waning arterial stiffness and endothelial function observed in women with PCOS. However, increased cardiovascular risk remains significant in women with PCOS even after adjustment for BMI. This finding indicates that adiposity itself in PCOS women cannot explain the increased CVD risk in PCOS women. This warrants further prospective study with hard cardiovascular outcome.

How to mitigate cardiovascular risk in women with PCOS?

Only answer to this question is screening for cardiovascular risk, especially subclinical cardiovascular risk in women with PCOS. At present, along with weight reduction, regular physical exercise and blood pressure measurement, CAC scoring is considered for screening purpose in women aged greater than 40 years as per 2019 ACC/AHA primary prevention guideline (Guan et al., 2022). But, it is conceivable that it takes time for the plaque to calcify in vascular intima. Therefore, it will be of more beneficial for the patients, if functional, non-invasive early, surrogate vascular markers may be considered for screening purpose such as pulse wave velocity, endothelial function testing. More emphasis might be given to operator-independent methodologies, which will help in screening large population.

CONCLUSION

It is evident from the previous sections that women with PCOS display enhanced arterial stiffness and endothelial dysfunction in comparison to age and BMI-matched healthy control group, though controversy exists in the literature. However, the existing traditional cardiovascular risk factors along with unique hormonal status in PCOS women, make them more prone to cardiovascular disease. It needs further prospective study with hard cardiovascular outcome to prove this point without any doubt. Moreover, genetic studies are warranted to establish the causality between this unique hormonal state and cardiovascular risk. It must be emphasized that regular cardiovascular screening might be advocated for this vulnerable population to prevent any major cardiovascular eventuality.

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