The Early Detection of Subclinical Left Ventricular Diastolic Dysfunction in Iraqi Women with Polycystic Ovarian Syndrome

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ABSTRACT:

BACKGROUND:

The left ventricular diastolic dysfunction (LVDD) in asymptomatic patients with polycystic ovarian syndrome (PCOS) has been documented by both pulsed wave Doppler and tissue Doppler echocardiography.

OBJECTIVE:

The aim of this study was to identify the earliest asymptomatic impairment of the left ventricular diastolic dysfunction in polycystic ovarian syndrome women.

PATIENTS AND METHODS:

This study is conducted by the Department of Physiology, College of Medicine, Al-Mustansiriya University in cooperation with the unit of Infertility and unit of Echocardiography at Al-Yarmook teaching hospital in Baghdad during the period from December 2015 to April 2017. A total number of 150 subjects were included in this study, 50 healthy subjects (control group) and 100 patients with polycystic ovarian syndrome with (mean age and standard deviation of 28.27 ± 7.27 years). Pulsed wave blood flow Doppler and tissue Doppler imaging were used for estimating left ventricular diastolic dysfunction.

RESULTS:

11% of the 100 PCOS women showed evidence of left ventricular diastolic dysfunction through impairment of mitral valve annular velocities and in the filling velocities of the left ventricle by pulsed wave Doppler, the ratio of peak early (E) filling velocity to the late (A) filling velocity (E/A ratio) was significantly lower in polycystic ovarian syndrome women with left ventricular diastolic dysfunction (0.78±0.17). By TDI the ratio of early (e´) mitral annular velocity to the late (a´) mitral annular velocity (e´/a´ ratio) was significantly reduced in polycystic ovarian syndrome women with the left ventricular diastolic dysfunction. Body mass index, waist circumference, waist-to-hip ratio, fasting blood sugar, fasting insulin, serum cholesterol, serum triglycerides, low density lipoprotein, very low density lipoprotein and homeostasis model assessment of insulin resistance were higher in polycystic ovarian syndrome group with left ventricular diastolic dysfunction.

CONCLUSION:

Diastolic dysfunction can develop early in patient with PCOS, and might be an early signal for cardiac involvement in this patient population.

KEYWORDS: Left ventricular diastolic dysfunction and polycystic ovarian syndrome.

INTRODUCTION:

Polycystic ovary syndrome (PCOS) is a heterogeneous disease of unknown cause [1,2]. PCOS is due to combination of environmental and genetic factors [3]. It is one of most common endocrine disorders in women during reproductive period between the ages of 14 - 45 years [4]. It affects 10% of women in reproductive age [5]. PCOS is characterized by chronic anovulation and hyperandrogenism [5, 6]. PCOS associated with other condition like obesity, type 2 diabetes, dyslipidemia, hypertension, heart disease, obstructive sleep apnea, endometrial cancer and metabolic syndrome [7]. A study published in the 2010 revealed that women with PCOS have an increased prevalence of insulin resistance (IR) and type 2 diabetes, even with normal body mass index (BMI) [8]. Obesity and insulin resistance is probably the major risk factors for the occurrence of cardiovascular disease in women with PCOS [9]. Left ventricular diastolic dysfunction (LVDD) is an early sign of cardiomyopathy in women with PCOS [10].

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The etiology of LVDD is multifactorial and is associated with hypertension, coronary artery disease, autonomic neuropathy, dyslipidemia, microangiopathy, oxidative stress and low-level inflammation and progression of endothelial dysfunction which leads to development of hypertension and cardiovascular disease [11].

Conventional echocardiography and tissue Doppler imaging parameters are widely used, quick, inexpensive, non-invasive and radiation free method to assess, evaluate and make accurate determination of left ventricular volume and ejection fraction. It is important for making a clinical decision and follow up [12]. Left ventricular diastolic dysfunction in PCOS patients can be diagnosed by tissue Doppler image before the onset of clinical signs of heart failure and before the presence of traditional echocardiographic indices of systolic myocardial dysfunction [13]. The aim of the study is to identify the earliest asymptomatic impairment of left ventricular diastolic function in PCOS women by both conventional Doppler echocardiographic parameters and tissue Doppler imaging.

SUBJECTS AND METHODS:

The study was done at Department of Physiology, Medical College of Al-Mustansiriya University in Cooperation with Infertility and Echocardiography units of Al-Yarmook teaching hospital during the period from December 2015 until April 2017.

A total number of 150 subjects were included in this study, 50 healthy subjects as control group and 100 patients with polycystic ovarian syndrome (PCOS) diagnosed by Rotterdam criteria 2003. All females were between the age of 16 and 45 years with mean age and standard deviation of (28.27±7.27 years).

The Rotterdam by European Society for Human Reproduction/American Society of Reproductive Medicine ESHRE/ASRM consensus group

In Rotterdam indicated presence of PCOS if any two out of three criterion are present in the nonappearance of other diseases that might reason these results [4].

1. Chronic anovulation and/or oligoovulation (oligomenorrhea or amenorrhea).
2. Hyperandrogenism (hirsutism, acne) clinical and/or biochemical.
3. PCOS by ultrasound (polycystic ovaries).

Exclusion criteria were Type 1 and 2 diabetes mellitus, systemic hypertension (systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg) at the time of visit or the use of antihypertensive drugs), valvular heart disease, heart failure, cardiac arrhythmia, renal disease and thyroid disease. Verbal consent was obtained from all women after explanation of the aim of the study. History interview and general physical examination were performed for all 150 women. Blood pressure measurement, Body mass index (BMI), waist and hip measurements, waist- to hip ratio (WHR). Blood sampling taking after an overnight fasting for oral glucose tolerance test (OGTT), fasting insulin level done by immunotech insulin level using immunoradiometric assay (IRMA) by gamma counter and lipid profile done by closed system called Automatic Biochemistry Analyser [14].

Echocardiographic measurements were done under the supervision of the specialist echo cardiologist at Al-Yarmook teaching hospital by the machine Philips CX50 ultrasound system USA 2009 with a transducer operating the 3.5 MHz, conventional echocardiography, 2-D echocardiography, motion or M-mode, pulsed-wave Doppler, continuous-wave Doppler and tissue Doppler imaging done for all subjects. These parameters were used to assess the left ventricular diastolic function in PCOS women. So that for early detection of subclinical left ventricular diastolic dysfunction (LVDD) in asymptomatic PCOS women, multiple diastolic functional parameters used included peak early filling velocity (E) (cm/sec) which reflects the period of active LV relaxation, peak late filling velocity (A) (cm/sec) which reflects LV-LA pressure gradient in diastole, influenced by LV relaxation, E/A ratio, isovolumetric relaxation time (IVRT) is the period from aortic valve closure to the opening of the mitral valve and deceleration time (DT) which is the time for which reduction of transmitral pressure gradient occurs. By tissue Doppler imaging (TDI) we measure lateral e´, lateral a´ (cm/sec), medial e´, medial a´(cm/sec), lateral and medial e´/a´ ratio and E/ e´ average ratio. The grading of LVDD was shown in (Table 1) and (Figure 1) demonstrates E/A ratio changes with progression of diastolic dysfunction [15, 16].

Table1: Defining the Grades of Diastolic Dysfunction.

			Grade I	Grade II	Grade III	Grade IV
Parameter	Units	Normal	Impaired relaxation	Pseuddonormal	Restrictive filling reversible	Restrictive filling irreversible
IVRT	ms	70-90	>90	60-90	<70	<70
E/A ratio	Unit-less	0.9-1.5	<0.9	0.9-1.5	>1.8	>2.0
Deceleration time	ms	140-240	>240	140-200	<140	<130

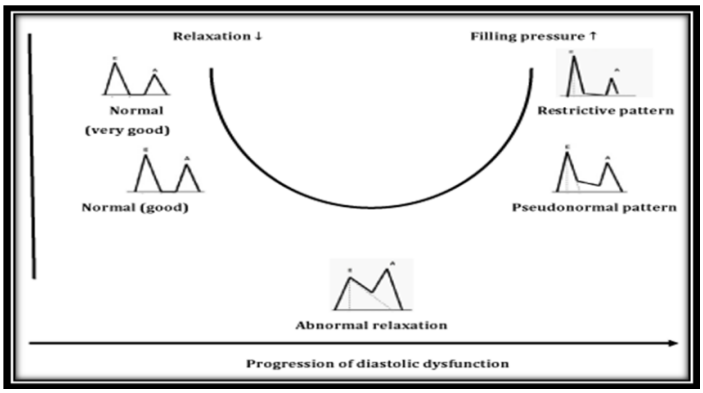

Figure 1: Progression of diastolic dysfunction.

RESULTS:

Our study revealed the percentage of subclinical LVDD in asymptomatic women with PCOS was 11% (11 PCOS women with LVDD, 89 PCOS women without LVDD) as shown in (Figure 2).

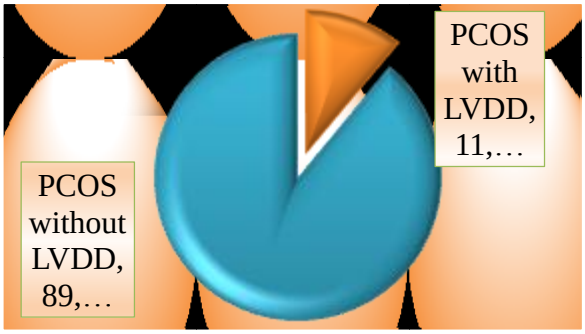

Figure 2: Percentage of PCOS women with and without LVDD.

Table 2 showed the clinical and metabolic characteristics of 150 women involved in this study, when we compared between 100 PCOS patients and 50 control subjects. The study showed that there were significant difference between two groups (control and PCOS) in BMI, fasting blood sugar, fasting insulin level, serum cholesterol, serum triglycerides, HDL, LDL, LDL/HDL and HOMA-IR with P-value < 0.05. As suspected PCOS women had significantly higher BMI, fasting blood sugar, fasting insulin level, cholesterol level, triglycerides, LDL, LDL/HDL and HOMA-IR while HDL level were significantly lower in PCOS woman than control group as shown in (Table 2). There were no significant difference in age (years), WHR, waist circumference and VLDL between control and PCOS group (Table 2).

Table 2: The clinical and metabolic parameters of PCOS patients compared with control women.

	PCOS	Control	P value
Age (years)	28.5±6.56 (16-45)	28.4±6.93 (16-45)	0.931
Body mass index (BMI) (Kg/m²)	30.26±5.80 (18.80-43.60)	28.46±3.77 (21.80-35.30)	0.047*
Waist circumference (cm)	88.10±10.48 (67-121)	85.70±9.28 (65-102)	0.172
Waist-Hip Ratio (WHR)	0.83±0.07 (0.70-1.20)	0.81±0.05 (0.68-0.90)	0.074
Fasting blood sugar (FBS) (mg/dL)	96.57±5.67 (83-110)	86.98±6.68 (70-100)	0.0001*
Fasting insulin (µu/ml)	16.07±3.34 (9.00-24.60)	7.81±1.95 (4.50-12.50)	0.0001*
Serum cholesterol (mg/dL)	202.88±30.52 (135-312)	165.32±16.28 (129-190)	0.0001*
Serum triglycerides (mg/dL)	150.78±34.03 (30-273)	116.92±32.14 (58-160)	0.0001*
HDL (mg/dL)	48.23±7.04 (30-67)	51.42±5.75 (40-66)	0.006*
LDL (mg/dL)	127.75±25.09 (75-220)	94.24±14.13 (57-120)	0.0001*
VLDL (mg/dL)	20.26±7.50 (6-45)	18.02±6.79 (6-35)	0.077
LDL/HDL	2.69±0.66 (1.40-5.00)	1.84±0.30 (0.86-2.40)	0.0001*
HOMAIR	3.73±0.84 (2.00-5.80)	1.65±0.46 (0.86-2.70)	0.0001*

♦ *** P-value at 0.05 levels.**

Regarding echocardiographic parameters (Table 3) showed the comparison between PCOS women and control group in M-mode measurements. There was no significant difference between two groups in M-mode echocardiographic parameters.

Table 3: The M-mode echocardiographic parameters of PCOS women compared with control group.

	PCOS	Control	P value
LVEDD (mm)	42.92±4.24 (33-55)	41.56±4.10 (33-53)	0.063
LVESD (mm)	27.77±2.91 (21-36)	26.84±3.55 (21-36)	0.089
EF (%)	63.61±6.02 (51-79)	65.02±5.53 (54-74)	0.167
IVS Thick (mm)	8.63±0.95 (7-12)	8.78±0.74 (8-10)	0.329
Aortic RD (mm)	23.59±3.71 (16-42)	23.26±2.81 (19-30)	0.580
LAD (mm)	29.69±4.25 (21-39)	29.02±5.42 (20-39)	0.409
RVD (mm)	27.69±3.18 (19-37)	27.38±3.61 (19-35)	0.592

♦ *** P-value at 0.05 levels.**

Table 4 shows the pulsed wave flow Doppler echocardiographic measurements. There were no significant differences between PCOS woman and control group in Peak early filling velocity (E) (cm/sec), peak late filling velocity (A) (cm/sec), E/A ratio, deceleration time (DT) (ms) and isovolumic relaxation time (IVRT) (ms).

Table 4: The Pulsed-wave Doppler echocardiographic parameters of PCOS women compared with control group.

	PCOS	Control	P value
E (cm/sec)	81.32±12.36 (50.40-119.00)	82.53±10.67 (64.60-106.00)	0.557
A (cm/sec)	59.71±13.83 (39.60-118.00)	59.64±7.38 (43.80-75.20)	0.976
E/A ratio	1.41±0.31 (0.45-2.50)	1.38±0.15 (1.10-1.70)	0.470
IVRT (ms)	59.20±15.29 (36-94)	57.16±10.05 (45-90)	0.394
DT (ms)	130.82±23.22 (90-199)	133.98±21.87 (99-184)	0.424

♦ *** P-value at 0.05 levels.**

Regarding tissue Doppler imaging measurements (TDI), the (Table 5) showed that there were no significant differences between PCOS women and control group and parameters measured by TDI.

Table 5: Tissue Doppler imaging (TDI) parameters of PCOS women compared with control group.

	PCOS	Control	P value
Lat é (cm/sec)	15.76±3.34 (6.70-24.90)	16.11±2.48 (11.10-22.20)	0.509
Lat á (cm/sec)	10.98±2.78 (7.20-18.20)	10.75±2.23 (7.12-15.60)	0.604
Lat é/á ratio	1.50±0.39 (0.55-2.41)	1.53±.30 (1.20-2.34)	0.619
Med é (cm/sec)	12.49±2.51 (5.13-18.50)	12.79±1.96 (8.60-17.50)	0.458
Med á (cm/sec)	9.35±2.22 (5.20-16.10)	9.42±1.72 (6.20-13.40)	0.850
Med é/ á ratio	1.39±0.36 (0.42-2.30)	1.37±0.17 (1.10-1.90)	0.601
é average (cm/sec)	14.12±2.65 (6.05-20.60)	14.45±1.81 (11.00-18.25)	0.435
á average (cm/sec)	10.17±2.23 (6.20-16.50)	10.08±1.61 (7.25-13.10)	0.789
E/Lat é ratio	5.34±1.18 (3.43-8.96)	5.21±0.96 (3.50-7.40)	0.513
E/Med é ratio	6.70±1.36 (4.30-10.40)	6.59±1.34 (4.23-9.95)	0.643
E/é average ratio	5.91±1.12 (3.99-8.79)	5.79±0.95 (4.09-7.79)	0.519

♦ *** P-value at 0.05 levels.**

PCOS with LVDD and PCOS without LVDD

When we compared between 11 PCOS women with LVDD and 89 women without LVDD, we found that there was significant increase in the age of PCOS women who have LVDD. Also there were significant increase in BMI, WHR, waist circumference, fasting blood sugar, fasting insulin level, cholesterol level, TG, LDL, VLDL and HOMA-IR. All these parameters were increased in PCOS women with LVDD (P-value < 0.05) as shown in (Table 6).

Table 6: The clinical and metabolic parameters in PCOS women with LVDD and PCOS women without LVDD.

	PCOS with LVDD	PCOS without LVDD	P value
Age (years)	33.45±4.72 (25-42)	26.57±7.04 (16-45)	0.002*
Body mass index (BMI) (Kg/m²)	34.48±3.86 (26.20-39.90)	29.74±5.80 (18.80-43.60)	0.010*
Waist circumference (cm)	100.73±9.46 (84-121)	86.54±9.53 (67-106)	0.0001*
Waist-Hip Ratio (WHR)	0.90±0.11 (0.77-1.20)	0.82±0.06 (0.70-0.99)	0.0001*
Fasting blood sugar (FBS) (mg/dL)	100.27±3.90 (95-106)	96.11±5.70 (83-110)	0.021*
Fasting insulin (µu/ml)	20.25±1.91 (17.10-23.50)	15.55±3.11 (9.00-24.60)	0.0001*
Serum cholesterol (mg/dL)	226.36±24.08 (185-254)	199.98±30.08 (135-312)	0.006*
Serum triglycerides (mg/dL)	170.36±24.33 (98-185)	148.70±33.33 (60-273)	0.040*
HDL (mg/dL)	46.45±7.53 (30-55)	48.45±6.99 (31-67)	0.378
LDL (mg/dL)	142.64±12.42 (113-155)	125.93±25.71 (75-220)	0.037*
VLDL (mg/dL)	25.36±7.75 (15-35)	19.63±7.27 (6-45)	0.016*
LDL/HDL	3.00±0.61 (2.40-4.50)	2.65±0.66 (1.40-5.00)	0.097
HOMAIR	4.84±0.47 (4.30-5.60)	3.59±0.78 (2.00-5.80)	0.0001*

♦ *** P-value at 0.05 levels.**

DISCUSSION:

Many studies have suggested increased cardiovascular disease risk in young and middle-aged women with PCOS like endothelial dysfunction and myocardial dysfunction [17, 18]. This study is the first one done in women with PCOS in reproductive period for evaluation of cardiovascular risk by echocardiography technology by both pulsed-wave Doppler and tissue Doppler imaging for detection of earliest asymptomatic impairment of LVDD in women with PCOS. So that our results showed the percentage of LVDD in asymptomatic women with PCOS was 11 % (out of 100 women with PCOS). This result is consistent with (Schannwell CM, et al, 2002) [10] that left ventricular diastolic dysfunction is an early sign of cardiomyopathy in women with PCOS. Also (Yarali H, et al, 2001) [17] and (Orio F, et al, 2004) [18] were they reported diastolic dysfunction in PCOS women.

The clinical and metabolic parameters of PCOS women compared with control subjects are shown in (table 2). There was statistically significant difference between two groups (control and PCOS) in BMI; this means PCOS patients tend to be more obese than control subjects. This result was consistence with (Dibello V, et al, 2006) [19] who they said that heart failure risk is more common in obese women than non obese women. There were significant higher fasting blood sugar (FBS), fasting insulin level, serum total cholesterol, serum triglycerides, LDL, LDL/HDL ratio and HOMA-IR, while that HDL level was significantly lower in PCOS group. Our results were consistent with (Dunaif A, 1997) [9] (Davi G, et al, 2002) [20] (Ovaille F, et al, 2002) [21].

Also some, not all studies have shown increased total cholesterol concentrations level in PCOS patients [22-24]. Our finding is consistent with study

done by (Orio F, et al, 2004) [18] who showed that women with PCOS had higher fasting glucose and insulin levels, Homeostasis model assessment of insulin resistance (HOMA-IR), total cholesterol, TG level, LDL-C and TG/HDL-C ratio and lower HDL level than controls. So that dyslipidemia is very common metabolic abnormality in PCOS women [23].

The echocardiographic measurements are used to assess the left ventricular diastolic function in PCOS women that we can diagnose 11 PCOS women out of 100 PCOS women who have subclinical and asymptomatic LVDD. There was no exact similar study to our study. But there are two studies done by (Selcoki Y, et al, 2010) [25] and (Tekin A, et al, 2009) [26] who they found that there were no significant differences between PCOS women and control group in echocardiographic measurements. Our study revealed that there were reversed lateral and medial e´/a´ velocities in PCOS women with LVDD. This consistence with (Park HS, et al, 2006) [27] who found that combination of lateral and medial (septal) reversed e´/a´ are useful for the detection of early stage of diastolic dysfunction from more advanced stages of diastolic dysfunction. (Colleagues and park) found that septal TDI tends to more estimate the severity of LVDD when compared with lateral TDI.

Our study revealed that 11 women with PCOS had LVDD out of 100 PCOS women diagnosed by pulsed-wave Doppler by reversed E to A velocity and by TDI by reversed lateral and medial e´/a´ velocities and E/A ratio, lateral e´/a´ and medial e´/a´ ratios are all less than one. All these 11 women with PCOS and LVDD had obesity, dyslipidemia and insulin resistance. These results are consistent with finding of (Wojciech Kosmala, et al, 2008) [28] who concluded that asymptomatic impairment of left ventricular function in young women is associated with obesity and insulin resistance rather than sex hormone abnormalities associated with polycystic ovaries.

Many studies finding correlate between heart disease and dyslipidemia in PCOS women [9], insulin resistance [22], increased left ventricular mass and diastolic dysfunction [17]. Also (Bjorntorp P, 1996) [29] said that the lipid profile showed higher cholesterol level and low density lipoprotein (LDL) level in PCOS women. Type 2 diabetes, obesity, hypertension, endothelial dysfunction, coronary artery disease, dyslipidimia and oxidative stress may lead to left ventricular systolic and diastolic dysfunction [30].

CONCLUSION:

Left ventricular diastolic dysfunction can develop in women with PCOS and may be an early signal for cardiac involvement in these patients population. PCOS women with LVDD have significantly higher level of cholesterol and LDL.

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