Comparison of clinical features and health manifestations in lean vs. obese Indian women with polycystic ovarian syndrome

ABSTRACT

AIMS: To study the prevalence of clinical manifestations in obese and lean polycystic ovarian syndrome (PCOS) women and their health hazards. **SETTINGS AND DESIGN:** This prospective study was carried out in a tertiary care infertility clinic from 1.7.2005 till 31.12.2007. **MATERIALS AND METHODS:** These women were diagnosed to have PCOS by the European Society of Human Reproduction and Embryology and the American Society of Reproductive Medicine, Rotterdam 2003 criteria. They were further divided into two groups according to their body mass index (BMI): Group A (n = 300), overweight and obese with BMI >23 and Group B (n = 150), normal weight and lean with BMI ≤23. **STASTICAL ANALYSIS AND RESULTS:** The prevalence of menstrual irregularities [79.2% vs. 44%, *P*= 0.000, 95% confidence interval (CI) = 0.26–0.44)] and clinical hyperandrogenism (74.2% vs. 50.6%, *P*= 0.000, 95% CI=0.14–0.32) was signifi cantly higher in the obese group, whereas android central obesity (waist to hip ratio >0.85) was similar in both groups, irrespective of body weight (47.7% vs. 38%, *P*= 0.056, 95% CI=0.06 to +0.18). Comparative data of various health manifestations in lean vs. obese women with POCS [Table 4]. Of the health risk manifestations, hypertension occurred in both groups with a similar frequency (41% vs. 35.5%, *P*= 0.261, 95% CI=0.03 to +0.15). Group A showed an increased prevalence of IGT (25% vs. 10%, *P*= 0.000, 95% CI= 0.13–0.29) and type two diabetes mellitus (11.7% vs. 6%, *P*= 0.000, 95% CI= 0.13–0.29) as compared with group B. endometrial hyperplasia (EH) also showed an increase prevalence in Group A compared with Group B (5.6% vs. 2%, *P*= 0.055, 95% CI= 0.01–0.08), although not statistically significant. **CONCLUSION:** PCOS emerges as a clinically heterogeneous condition with increased prevalence of health risks such as hypertension, diabetes and EH. Of these, diabetes and EH appear to be more prevalent in the obese, putting them at a greater risk of morbid problems at a much younger age than the lean ones.

KEY WORDS: Android obesity, anovulation, body mass index, diabetes, endometrial hyperplasia, hyperandrogenism, hypertension, impaired glucose tolerance, polycystic ovarian syndrome

Abha Majumdar, Tejshree A Singh
Departments of Obstetrics and Gynecology, Sir Ganga Ram Hospital, Kolmet Hospital and Research Centre, New Delhi, India

Address for correspondence:
Dr. Tejshree A. Singh, 28/76, 3rd Floor, West Patel Nagar, New Delhi - 1100 008, India. E-mail: drtejsingh001@yahoo.co.in

Received: 01.07.08
Review completed: 10.01.09
Accepted: 31.03.09

DOI: 10.4103/0974-1208.51336

INTRODUCTION

Polycystic ovarian syndrome (PCOS) affects four to 12% women of reproductive age.[1] In 1935, Stein and Leventhal first described the association of polycystic ovaries, amenorrhea, hirsutism, and obesity. The key features necessary for the diagnosis of PCOS were detailed at a conference convened by the National Institute of Health in 1990 and they were menstrual dysfunction and hyperandrogenism, with exclusion of other causes of hyperandrogenism (congenital adrenal hyperplasia, androgen-secreting tumors, and hyperprolactinemia). Probable criteria included perimenarchal onset, insulin resistance, elevated leutenizing hormone to follicle-stimulating hormone ratio and polycystic ovaries by ultrasonography (USG).[1]

PCOS was redefined at a joint consensus meeting of the European Society of Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM), held in Rotterdam in May 2003. This included the presence of two of the following three criteria: (a) oligo and/or anovulation, (b) polycystic ovaries on USG and (c) hyperandrogenism (clinical and/or biochemical), with the exclusion of other etiologies. The morphology of the polycystic ovary has been redefined as an ovary with 12 or more follicles measuring 2–9 mm in diameter and/or increased ovarian volume (more than 10 cm^3).[2]

Recent insights into the pathophysiology of PCOS have shown that insulin resistance is a key feature and predisposes to type two diabetes mellitus in the long run. Higher levels of plasminogen activator inhibitor (PAI) type one, decreased vascular relaxation and endothelial dysfunction

result in increased risk of hypertension and coronary artery disease. Chronic anovulation leads to a higher risk of developing endometrial hyperplasias (EHs), with or without cytological atypia as a sequel to unopposed estrogen exposure in the absence of progesterone.[1]

The aim of this study was to study the prevalence of clinical manifestations and health risks in obese and lean PCOS women; primarily, impaired glucose tolerance (IGT) and diabetes, menstrual irregularity, and clinical hyperandrogenism and, secondarily, EH, android obesity and hypertension.

MATERIALS AND METHODS

Observational study

To calculate the sample size, predicted prevalence of diabetes (7.5% vs. 1.5%) and IGT (31% vs. 10.3%) in the two groups obese vs. nonobese was taken into account. Sample size calculation was performed using software SPSS13 (SPSS Inc., 233 South Wacker Drive, 11th floor, Chicago IL 60606-6412), taking the power of the study to be 100% for the primary manifestations/risks.

Description of the source population: This study was conducted on northern Indian women in the reproductive age group (18–42 years) attending an infertility clinic at a tertiary hospital from 1.7.2005 till 31.12.2007.

Menstrual history was taken. Patients were screened for clinical signs of hyperandrogenism (acne, oily skin, and hirsutism) and transvaginal USG (probe 7 Megahertz) was undertaken to look for evidence of polycystic ovaries.

Eligibility criteria: Of all the women attending the infertility clinic, 450 women satisfying the ESHRE and ASRM criteria for PCOS were included in our study.[2]

These women were further separated into two groups according to their body mass index (BMI): Group A, obese and overweight – BMI > 23 (n = 300) and Group B, normal weight and lean – BMI ≤ 23 (n = 150). The World Health Organization committee examined data from 10 Asian countries and thus narrowed the range for acceptable, normal, or optimum BMI to 18.5–23 kg/m^2 for the Asian population.[3]

Technical information: Work-up of patients

1. Menstrual history.
2. Screening for clinical signs of hyperandrogenism (acne, oily skin, and hirsutism). Only 17-hydroxy progesterone (17-OHP) and dehydro-epiandrosterone sulfate (DHEAS) levels were examined to rule out congenital adrenal hyperplasia. All patients had normal values of 17-OHP (<2 ng/ml) and DHEAS (<7 ng/ml).
3. Height was measured without shoes against a wall-fixed tape.[4]
4. Weight with light clothing and without shoes on a platform scale with a 1.5 kg subtraction to correct for clothing weight. The BMI was calculated as weight/height^2 (kg/m^2).[4]
5. Android obesity (waist to hip ratio >0.85): Waist circumference was measured at the level of the umbilicus without clothing and in standing position in inches. Hip circumference was measured at the utmost circumference with undergarment in inches.[4]
6. Blood pressure: Two separate measurements 6 h apart.[5]
   - Prehypertension: Systolic pressure ranging from 120 to 139 mmHg or a diastolic pressure ranging from 80 to 89 mmHg.
   - Stage 1 hypertension: Stage 1 hypertension is a systolic pressure ranging from 140 to 159 mmHg or a diastolic pressure ranging from 90 to 99 mmHg.
   - Stage 2 hypertension: The most severe hypertension, stage 2 hypertension, is a systolic pressure of 160 mmHg or higher or a diastolic pressure of 100 mmHg or higher.
7. Oral glucose tolerance test: 100 g of glucose, venous sample (ACOG criteria).[6]
   - IGT: Fasting glucose levels >110 mg/dl (6.1 mmol/l) but <126 mg/dl (7.0 mmol/l); 2-h postglucose load levels: 140–200 mg/dl.
   - Diabetes mellitus: Fasting glucose levels >126 mg/dl (7.0 mmol/l); 2-h postglucose load levels >200 mg/dl.
8. USG on day 3 of the menstrual cycle or withdrawal of bleed.
9. Hysteroscopy D+C: Those with endometrial thickness (ET) on day 3 of the cycle more than 4 mm on USG underwent hysteroscopy D+C and histopathological evaluation of the endometrium.

There were no dropouts from the clinical trial.

The statistical methods that were used for categorical variables were χ^2 test and Fischer's exact test (software SPSS13).

RESULTS

Age-wise distribution of patients [Table 1].

All the 450 women showed ultrasound evidence of polycystic ovaries. Three hundred forty-four women (76.4%) showed oligo/anovulation, 299 women (66.4%) showed hyperandrogenism (clinical) and 175 women (38.8%) showed both the features.

Distribution of patients according to BMI [Table 2].

Comparative data of various clinical features in lean vs. obese women with POCS [Table 3].

Table 1: Age-wise distribution of patients

Age group	No. of patients (n = 450)		
	Group A	Group B	Total (%)
	Obese (n = 300)	Lean (n = 150)	
Less than 20	02	02	04 (0.9)
21 − 25	43	25	68 (15.1)
26 − 30	157	79	236 (52.5)
31 − 35	81	31	112 (24.8)
36 − 40	17	11	28 (6.2)
More than 41	-	02	02 (0.5)

Mean age in years 29.1 28.4

Table 2: Distribution of patients according to body mass index

Body mass index	No. of patients n = 450 (%)
Group A	
Obese:	
More than 27.5	169 (37.5)
Overweight:	
23 − 27.5	131 (29.1)
Total	300 (66.6)
Group B	
Normal weight:	
18.5 − 23	134 (29.8)
Lean:	
Less than 18.516 (3.6%)	
Total	150 (33.4)

The prevalence of menstrual irregularities [79.2% vs. 44%, *P*=0.000, 95% confidence interval (CI) = 0.26–0.44)] and clinical hyperandrogenism (74.2% vs. 50.6%, *P*=0.000, 95% CI=0.14–0.32) was significantly higher in the obese group, whereas android central obesity (waist to hip ratio >0.85) was similar in both groups, irrespective of body weight (47.7% vs. 38%, *P* = 0.056, 95% CI −0.06 to +0.18).

Comparative data of various health manifestations in lean vs. obese women with POCS [Table 4].

Of the health risk manifestations, hypertension occurred in both groups with a similar frequency (41% vs. 35.5%, *P*=0.261, 95% CI=0.03 to +0.15). Group A showed an increased prevalence of IGT (25% vs. 10%, *P*= 0.000, 95% CI= 0.13–0.29) and type two diabetes mellitus (11.7% vs. 6%, *P*= 0.000, 95% CI= 0.13–0.29) as compared with group B. EH also showed an increase prevalence in Group A compared with Group B (5.6% vs. 2%, *P*= 0.055, 95% CI= 0.01–0.08), although not statistically significant (because of very few cases).

DISCUSSION

Most PCOS patients are inherently insulin resistant, with obesity seen in many, only adding to this problem. A substantial proportion of PCOS patients have abnormalities on the oral glucose tolerance testing at the time of diagnosis.

Table 3: Comparative data of various clinical features in lean vs. obese women with polycystic ovarian syndrome

	Group A	Group B	*P*-value
	Obese n = 300 (%)	Lean n = 150 (%)	Odds ratio 95%CI
Mean age in years	29.1	28.4	
Waist to hip ratio:			*P*−0.056 (OR – 1.486, 0.99−2.21)
> 0.85	143 (47.7)	57 (38)	(Power 88%)
≤ 0.85	157 (52.3)	93 (62)	
Menstrual cycles:			*P*−0.000 (OR – 4.88, 3.18-7.48)
Abnormal	238 (79.2)	66 (44)	(Power 100%)
Withdrawal bleed	126 (42)	14 (9.4)	
Delayed	78 (26)	21 (14)	
Early	23 (7.6)	27 (18)	
Variable	11 (3.6)	04 (2.6)	
Normal	62 (20.8)	84 (56)	
Oligo-ovulation	18 (6)	22 (14.6)	
Normal ovulation	44 (14.8)	62 (41.4)	
Clinical hyperandrogenism:			*P*−0.000 (OR–2.82, 1.86–4.25)
Clinical hyperandrogenism present	223 (74.2)	76 (50.6)	(Power 100%)
Hirsutism	101 (33.6)	42 (28)	
Acne & oilyskin	122 (40.6)	34 (22.6)	
Hirsutism, acne & oily skin	56 (18.6)	25 (16.6)	
Clinical hyperandrogenism absent	77 (25.8)	74 (49.4)	

OR = Odds ratio

In 2000, a multicentric study involving seven urban cities (Chennai, Bangalore, Hyderabad, Mumbai, Calcutta, and New Delhi) in India among the age group of 20–40 years indicated that the prevalence rate of obesity was 31%. Our study showed a 37.5% prevalence rate of obesity in women with PCOS.[7]

Obese PCOS patients have a 31% rate of IGT and 7.5% met the criteria for type two diabetes mellitus.[8] Nonobese PCOS patients have a 10.3% prevalence of IGT and 1.5% of type two diabetes mellitus, which is three times that of the general population.[8] PCOS women are at a significantly increased risk for IGT and type two diabetes mellitus at all weights and at a young age.[8]

These results were confirmed by another United States study (35% women with PCOS had IGT and 10% had non-insulin dependant diabetes mellitus (NIDDM) at the time of initial study).[9] The conversion from IGT to NIDDM is

Table 4: Comparative data of various health manifestations in lean vs. obese women with polycystic ovarian syndrome

	Group A	Group B	*P*-value
	Obese n = 300 (%)	Lean n = 150 (%)	Odds ratio 95%CI
Hypertension			*P*–0.261 (OR – 1.27, 0.84-1.91) (Power 58%)
Normotensive	177 (59)	97 (64.8)	
Prehypertensive	69 (23)	44 (29.2)	
Hypertensive	54 (18)	09 (6)	
Stage 1	32 (10.6)	07 (4.6)	
Stage 2	22 (7.4)	02 (1.4)	
PreHT + HT	123 (41)	53 (35.2)	
Diabetes	*P*–0.000 (OR – 3.1, 1.85–4.99)		
No diabetes	190 (63.2)	126 (84)	(Power 100%)
IGT	75 (25)	15 (10)	
Diabetes	35 (11.8)	09 (6)	
IGT + diabetes	110 (36.8)	24 (16)	
Endometrium			
Day 2 ET < 4 mm on USG	226 (75.4)	134 (89.2)	
Day 2 ET > 4 mm on USG	74 (24.6)	16 (10.6)	
No endometrial hyperplasia	57 (19)	13 (8.6)	
Endometrial hyperplasia	17 (5.6)	03 (2)	*P*–0.055
Without atypia	13 (4.4)	03 (2)	(OR – 2.8, 1.54–4.91) (Power 98%)
With atypia	04 (1.2)	-	

HT = Hypertensive, IGT = Impaired glucose tolerance, ET = Endometrial thickness

accelerated in PCOS.[9] The fasting glucose concentration does not reliably predict the glucose concentration at 2 h after an oral glucose challenge, particularly among those with IGT, the subgroup at the highest risk for subsequent development of NIDDM.[9]

Women with PCOS, particularly those with a high BMI, therefore, should periodically have an OGTT as the frequency of impaired glycemic control is high and the rate of conversion from normal glucose tolerance to IGT or from IGT to NIDDM is substantial.[10]

The prevalence of glucose intolerance is significantly higher in PCOS women (~30%) than in concurrently studied age ethnicity and weight-matched ovulatory control women (~10%).[11]

Among the PCOS subjects screened from the Mediterranean region, 15.7 and 2.5% displayed IGT and type 2 diabetes, respectively. Metabolic and hormonal characteristics of the IGT group also included hyperandrogenemia and significantly higher cortisol and androstenedione responses to 1-24 ACTH stimulation. One important finding was that lower birth weight and earlier age of menarche were associated with IGT in PCOS. Frequency of hirsutism, oligomenorrhea, acne and acanthosis nigricans did not characterize women with IGT.[12]

Another European study found only a 6.4% rate of IGT and no cases of type two diabetes mellitus.[13] This discrepancy may be related to a significant difference in the severity of obesity between the studies.[14]

Also, there is a 10-fold increased risk of developing gestational diabetes mellitus in women with PCOS as compared with the general population (baseline risk 3%).[15]

A national survey of diabetes and IGT conducted in 2000 AD in six major cities of India showed a 13.1% prevalence of IGT and 5% prevalence of diabetes in the younger age group (20– 40 years) of the general population.[7] Another study found that the prevalence rates of diabetes were 3.5%, hypertension 11%, central obesity 29%, overweight 41%, and dyslipidemia 24% in urban women in Delhi.[16] Our study showed a significantly higher prevalence of IGT (25% vs. 10%, *P*=0.000, RR 2.5*)* and type two diabetes mellitus (11.7% vs. 6%, *P*=0.000, RR 1.95) in obese PCOS women with respect to lean ones. These prevalence rates are higher than the prevalence rates reported in population-based studies of normal women of this age, as given above. It is thus clear that PCOS is a major risk factor for IGT and type two diabetes in women, more predominantly in the obese. Diabetes and IGT showed a positive and independent association with age, BMI, waist to hip ratio (WHR), and family history of diabetes.[7]

Apart from the increased risk of type two diabetes mellitus in PCOS patients, there are multiple other metabolic abnormalities that put them at a higher risk for cardiovascular disease. Many,[17,18] but not all,[19,20] studies have shown either a greater prevalence of diagnosed hypertension or higher ambulatory blood pressure in PCOS. Women with PCOS may also have higher levels of PAI type one,[21] decreased insulin-induced vascular relaxation[22] and endothelial dysfunction.[23]

The increased daytime blood pressures in women with PCOS and greater increases in pulse rate from night to daytime recordings persisted after adjusting for BMI, body fat distribution, and insulin resistance. Thus, women with PCOS have an increased prevalence of labile blood pressure, which may indicate a prehypertensive state, adding a further risk factor for cardiovascular disease.[17] Despite profound insulin resistance and hyperinsulinemia, women with PCOS do not have increased arterial pressure or left ventricular mass.[19]

The ICMR study in 1994 demonstrated 25 and 29% prevalence of hypertension (criteria ≥140/90 mmHg) among males and females, respectively, in urban Delhi.[24] The prevalence of hypertension (>140/90 mmHg) in urban women in northern India was 22.6%.[25] Multivariate logistic regression analysis showed that age (odds ratio 1.16), BMI (1.68) and obesity were strongly associated with hypertension.[25]

Our study showed a similar frequency of prehypertension in obese and lean PCOS women (23% vs. 29.2%, RR 0.8) and higher prevalence of frank hypertension in obese women (18% vs. 6%, RR 3). Combining the prevalence rates of prehypertension and hypertension, we get the following values (41% vs. 35.5%, *P*=0.261, 95% C I=0.03 to + 0.15). These prevalence rates are similar to the prevalence rates reported in population-based studies of normal women of this age.

As an extension of these data on risk factors, two retrospective studies of patients undergoing coronary angiography found women with a significant history of hirsutism to be more likely to have coronary artery disease.[26] Also, women with polycystic ovaries on ultrasound had more extensive coronary artery disease at catheterization than those without such ultrasound findings.[26] Lastly, PCOS patients have been shown to have increased carotid intimal media thickness[27] and an almost six-fold increased prevalence of coronary artery calcification[28] vs. age-matched control subjects.

Chronic anovulation and hyperandrogenism are clinical hallmarks of women with PCOS. Owing to anovulation, the endometrium in PCOS is exposed to the prolonged mitogenic effects of estrogen, unopposed by the inhibitory effects of progesterone present in the luteal phases of normal menstrual cycles. Thus, anovulation and PCOS are recognized risk factors for EH, with or without cytological atypia.[29,30]

The ET on ultrasound correlates positively with EH. In cases with day 3 ET on USG >7 mm, the prevalence of EH varies from 35.7% to 45.6%.[29,30] Most cases were simple EH and only 1.75% was simple EH with atypia. Age, BMI and WHR did not predict EH, whereas the endometrial hyperechogenic pattern was a clinical predictor of EH with borderline significance. In conclusion, this study demonstrated that almost half of the anovulatory women with amenorrhea had EH. In view of these findings, an endometrial biopsy should be performed in all women with this disorder.[30]

A recent prospective study of 56 PCOS patients was conducted with the aim of predicting EH. The author found high prevalence of EH in these patients (35.7%). Of the 20 cases of EH, 12, three, and five were simple hyperplasia, complex hyperplasia, and hyperplasia with cytological atypia, respectively. Women affected were older (30–40 years) and reported amenorrhea of 1–4 year duration. Logistic regression analysis revealed that ultrasonographic ET and intermenstrual interval were the only predictors of hyperplasia.[31]

Our study revealed an increase in prevalence of EH in obese compared with lean PCOS patients (*P*=0.055, RR 2.8). Atypical EH in obese group with withdrawal bleeding (four cases) was seen.

Cancer incidence rates in a Mayo Clinic cohort of 1270 women with chronic anovulation, as defined by ovarian appearance consistent with PCOS and clinical evidence of chronic anovulation, were compared with population incidence rates. The relative risk for subsequent endometrial cancer associated with this syndrome was 3.1. Increased risk was also noted for premenopausal and postmenopausal cancer.[32]

The true risk of endometrial disease in women with PCOS is difficult to ascertain. Studies have been limited to a relatively small number of cases of endometrial cancer identified specifically in PCOS. Furthermore, the heterogeneous presentation of the syndrome makes it impossible to ascertain which factor (hyperinsulinemia, obesity, and hormonal imbalance) has the most relevant role in the increased risk. Clinically, it is generally accepted that in oligoamenorrheic or amenorrheic women with PCOS, the induction of withdrawal bleeding to prevent hyperplasia is a prudent management.

Comparative data of various studies in women with PCOS [Table 5].

CONCLUSION

Thus, PCOS emerges as a clinically heterogeneous condition with increased prevalence of menstrual irregularities and clinical hyperandrogenism in the obese. Prevalence of hypertension and altered waist to hip ratio is independent of obesity. IGT, diabetes, and EH appear to be more prevalent in the obese, putting them at a greater risk of having morbid problems at a much younger age than the lean ones and, therefore, needing more rigorous management. It is important therefore that those caring for these patients understand not only the management issues pertinent to

Table 5: Comparative data of various studies in women with polycystic ovarian syndrome

Study	HT%	IGT%	Diabeties%	EH%
Present study, 2007				
Group A	41	25	11.7	5.6
Group B	35.5	10	06	02
Legro *et al*, 1999				
Obese	-	20.7	06	-
Lean	-	10.3	1.5	-
Ehrmann *et al*,1999	-	35	10	-
Elting *et al*, 2001	09	-	2.3	-
Gambineri *et al*, 2004	-	15.7	2.5	-

their specialty but also appreciate the other potential health risks in these women and counsel accordingly.

ACKNOWLEDGMENT

The authors wish to thank Dr. S. Saluja, Senior Consultant and Head, Department of Neonatology, Sir Ganga Ram Hospital, New Delhi for his help in statistics.

REFERENCES

1. E Medicine Article on PCOS by Kathy Silvermann and Elizabeth M Aldermann. Available from: http://www emedicine. Com /linkus/htm. modification by Robert J Ferry Jr, MD, , University of Tennessee Health Science Center at Memphis and St Jude Children's Research Hospital; Updated: [last retrieved on 2008 Jul 10].
2. Bonnar J, Dunlop W, editors. Recent advances in obstretics and gynecology Vol 23. London: Royal Society of Medicine Press Limited; 2005.
3. Choo V. WHO reassesses appropriate body-mass index for Asian populations. The Lancet 2002;360:235.
4. G. Sotoudeh, SR Mirdamadi, F Siassi, S Khosravi and M Chamari. Relationships of overweight and obesity with hormonal and metabolic parameters in hirsute women. Acta medica iranica 2003;41:37-44.
5. Mayo Clinic Staff (2008). "High blood pressure (hypertension): Tests and diagnosis". Mayoclinic.com. [last retrieved on 2008 Sep 11].
6. Report of Expert Committee on the Diagnosis and Classification of Diabetes Mellitus Diabetes Care 26:S5-S20, 2003 by the American Diabetes Association, Inc.
7. Snehalatha C, Ramchandran A, Kapur A, Vijay V. Age-specific prevalence and risk associations for impaired glucose tolerance in urban southern Indian population. J Assoc Physicians India 2003;51:766-9.
8. Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: A prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 1999;84:165-9.
9. Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care 1999;22:141-6.
10. Norman RJ, Masters L, Milner CR, Wang JX, Davies MJ. Relative risk of conversion from normoglycaemia to impaired glucose tolerance or non-insulin dependent diabetes mellitus in polycystic ovarian syndrome. Hum Reprod 2001;16:1995-8.
11. Quintana B, Chinchilli V, Sieber J, Fultz P, George N, Dunaif A. High risk of glucose intolerance (GI) in women with oligomenorrhea (oligo) or with polycystic ovary syndrome (PCOS). Abstract book of the 77th Annual Meeting of The Endocrine Society, June 1995, Washington, D.C. Abstract#OR3-5, p.50.
12. Gambineri A, Pelusi C, Manicardi E, Vicennati V, Cacciari M, Morselli-Labate AM, *et al.* Glucose Intolerance in a Large Cohort of Mediterranean Women with Polycystic Ovary Syndrome. Diabetes 2004;53:2353-8.
13. Ciampelli M, Fulghesu AM, Cucinelli F, Pavone V, Ronsisvalle E, Guido M, Caruso A, Lanzone A. Impact of insulin and body mass index on metabolic and endocrine variables in polycystic ovary syndrome. Metabolism 1999;48:167-72.
14. Ciampelli M, Fulghesu AM, Lanzone A. Comment on "Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome." J Clin Endocrinol Metab 1999;84:2974-5.
15. Glueck CJ, Wang P, Kobayashi S, Phillips H, Sieve-Smith L. Metformin therapy throughout pregnancy reduces the development of gestational diabetes in women with polycystic ovary syndrome. Fertil Steril 2002;77:520-5.
16. Singhi M, Prabhakaran D, Goenka S, Jeemon P, Chaturvedi V, Reddy KS. Adverse risk profile for cardiovascular diseases in Asian Indian women. Presentation made at Forum 9, Mumbai, India, 12-16 September 2005.
17. Holte J, Gennarelli G, Berne C, Bergh T, Lithell H. Elevated ambulatory day-time blood pressure in women with polycystic ovary syndrome: A sign of a pre-hypertensive state? Hum Reprod 1996;11:23-28.
18. Elting MW, Korsen TJ, Bezemer PD, Schoemaker J. Prevalence of diabetes mellitus, hypertension and cardiac complaints in a follow-up study of a Dutch PCOS population. Hum Reprod 2001;16:556-60.
19. Zimmermann S, Phillips RA, Dunaif A, Finegood DT, Wilkenfeld C, Ardeljan M, Gorlin R, Krakoff LR. Polycystic ovary syndrome: Lack of hypertension despite profound insulin resistance. J Clin Endocrinol Metab 1992;75:508-13.
20. Sampson M, Kong C, Patel A, Unwin R, Jacobs HS. Ambulatory blood pressure profiles and plasminogen activator inhibitor (PAI-1) activity in lean women with and without the polycystic ovary syndrome. Clin Endocrinol (Oxf) 1996;45:623-9.
21. Velazquez EM, Mendoza SG, Wang P, Glueck CJ. Metformin therapy is associated with a decrease in plasma plasminogen activator inhibitor-1, lipoprotein(a), and immunoreactive insulin levels in patients with the polycystic ovary syndrome. Metabolism 1997;46:454-7.
22. Kelly CJ, Speirs A, Gould GW, Petrie JR, Lyall H, Connell JM. Altered vascular function in young women with polycystic ovary syndrome. J Clin Endocrinol Metab 2002;87:742-6.
23. Paradisi G, Steinberg HO, Hempfling A, Cronin J, Hook G, Shepard MK, Baron AD. Polycystic ovary syndrome is associated with endothelial dysfunction. Circulation 2001;103:1410-5.
24. ICMR Task force project on Collaborative study of coronary Heart Study.
25. Singh RB, Beegom R, Mehta AS, Niaz MA, De AK, Haque M, *et al.* Prevalence and risk factors of hypertension and age-specific blood pressures in five cities: A study of Indian women. NKP Salve Institute of Medical Sciences, Nagpur, India. Five City Study Group. Int J Cardiol 1998;63:165-73.
26. Birdsall MA, Farquhar CM, White HD. Association between polycystic ovaries and extent of coronary artery disease in women having cardiac catheterization. Ann Intern Med 1997;126:32-5.
27. Talbott EO, Guzick DS, Sutton-Tyrrell K, McHugh-Pemu KP, Zborowski JV, Remsberg KE, Kuller LH. Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. Arterioscler Thromb Vasc Biol 2000;20:2414-21.
28. Christian RC, Dumesic DA, Behrenbeck T, Oberg AL, Sheedy PF 2nd, Fitzpatrick LA. Prevalence and predictors of coronary artery calcification in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2003;88:2562-8.
29. Anthony P. Cheung Ultrasound and Menstrual History in Predicting Endometrial Hyperplasia in Polycystic Ovary Syndrome Obstetrics and Gynecology. The American College of Obstetricians and Gynecologists. 2001;98:325-31.
30. Tingthanatikul Y, Choktanasiri W, Rochanawutanon M, Weerakeit S. Prevalence and clinical predictors of endometrial hyperplasia in anovulatory women presenting with amenorrhea. Gynecol Endocrinol 2006;22:101-5.
31. Cheung AP. Ultrasound and menstrual history in predicting endometrial hyperplasia in polycystic ovary syndrome. Obstet Gynecol 2001;98: 325-31.
32. Coulam CB, Annegers JF, Kranz JS. Chronic anovulation syndrome and associated neoplasia. Obstet Gynecol 1983;61:403-7.

Source of Support: Nil, **Conflict of Interest:** None declared.