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Correlation Between Insulin Resistance Indices And Endometrial Thickness To Predict Metabolic Syndrome & Ovulatory Dysfunction In Phenotypes Of Polycystic Ovarian Syndrome In South Indian Population

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Abstract:

Study objective: *Tocorrelate between Insulin Resistance Indices and Endometrial Thickness to predict Metabolic syndrome & ovulatory dysfunction in Phenotypes of Polycystic Ovarian Syndrome in south Indian population.*
Methods: *Forty reproductive-aged women (18–35 years old) who met the Rotterdam criteria for PCOS were enrolled in the Gynaecology outpatient department at our hospital were included in the study. The subjects were categorised based on the Rotterdam criteria into 4 phenotype groups. For all study participants, endometrial thickness and the insulin resistance indices was calculated using the biochemical parameters. The data was analyzed by Pearson's correlation coefficient for relationship between variables. Statistical analyses were performed with the help of SPSS software. For all statistical analyses the p value was significant when p <0.05.*
Results:*Correlation between endometrial thickness & insulin resistance indices in PCOS Phenotype A, phenotype -C & phenotype-D samples: The indices VAI, LAP, FAI, TyG& SPISE showed negative correlation with endometrial thickness. In PCOS Phenotype B samples: The indices LAP, FAI & SPISE showed negative correlation whereas the indices VAI &TyG showed positive correlation with endometrial thickness with the Pearson's correlation coefficient value(R) of -0.99 with p value of <0.01 & value(R) of -0.98 p value of <0.02 respectively showing statistically significant.*
Conclusion:*In PCOS phenotypes, especially with PCOS Phenotype B there is a substantial correlation between the insulin resistance indices & endometrial thickness. They are simple and affordable markers that have a good sensitivity and specificity for the diagnosis of metabolic syndrome & ovulatory.*

Introduction:

Women of childbearing age are disproportionately affected by polycystic ovarian syndrome(PCOS), one of the most prevalent endocrine diseases& the research on the etiology of PCOS is still ongoing. Polycystic ovarian syndrome (PCOS) also referred to as Stein–Leventhal syndrome, is a heterogeneous endocrine disorder in women of reproductive age and is associated with a broad range of health conditions including hypertension, dyslipidemia, insulin resistance, hyperandrogenemia, and type 2 diabetes mellitus (T2DM) (1). Globally, t[1]he prevalence of PCOS is estimated to be between 5.5% and 12.6% in women in the age group of 17–45 years. (2) In India, the prevalence estimates are between 8.2% and 22.5% depending on the diagnostic criteria used (2). After excluding out other endocrine conditions, the NIH (National Institute of Health) guidelines of 1990 categorized women with hyperandrogenism and oligo-anovulation as having polycystic

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ovarian syndrome. The second definition was provided by the Rotterdam expert group and included the presence of two of the three characteristics: clinical or biochemical hyperandrogenism, oligo-anovulation, and ultrasound-detected polycystic ovaries.A number of etiological factors, including obesity, insulin resistance, and hereditary factors, have been associated to polycystic ovarian syndrome, which can manifest before puberty (3). Because of increased insulin resistance and abdominal obesity, people with PCOS are more likely to develop Type 2 Diabetes mellitus. The metabolic components of this condition include decreased glucose tolerance, obesity, hyperlipidemia, and an increased risk of type 2 diabetes mellitus. Insulin resistance is also a contributory factor (4,5). After consuming food, insulin levels often momentarily increase, causing the liver and muscles to absorb glucose from the blood and utilise it as fuel. This leads to low insulin and blood glucose levels. Normal insulin sensitivity causes normal glucose level and normal insulin levels in a fasting blood test; normal insulin resistance causes normal blood glucose but elevated insulin levels. A surplus of insulin, induces inflammation and weight gain which can also lead to Type 2 diabetes and cardiovascular problems, is a physiological component that underlies PCOS (6,7). As hyperinsulinaemia plays a significant role in the onset and clinical presentation of polycystic ovary syndrome (PCOS), it is important to recognize that plasma insulin concentrations reflect both the rate at which insulin is secreted from beta cells, and the rate at which it is cleared from plasma (8). Women with Polycystic ovary syndrome (PCOS) generally develop Insulin Resistance due to abnormal insulin signalling and metabolic in insulin responsive tissues. The incidence of IR in PCOS is particularly high and has a considerable adverse effect on health (9).

The Endometrial Thickness (ET) on routine gynaecological ultrasound is of significant importance throughout a woman's reproductive cycle (10). Studies have demonstrated that alterations in gene expression in the endometrium & uncontrolled endocrine and metabolic alterations in women with Polycystic Ovary Syndrome (PCOS) can lead to the development of atypical Endometrial Hyperplasia and Endometrial Induced Fertility (11,12).

Hyperinsulinaemia also has a detrimental effect on endometrial function, with a higher incidence of implantation failure, and indicates that endometrial histomorphometric abnormalities persist and are associated with androgen and insulin concentrations, regardless of progesterone supplementation in PCOS (13,14).

The aim of our study is to Correlate between Insulin Resistance Indices and Endometrial Thickness to predict Metabolic syndrome & ovulatory disfunction in Phenotypes of Polycystic Ovarian Syndrome in south Indian population.

Materials and Methods:

Study design: After receiving approval from the institutional ethics committee with reference number RRMCH-IEC/16/2022, the current pilot study was carried out in the Obstetrics and Gynecology Department at Rajarajeswari Medical College and Hospital. Forty reproductive-aged women (18–35 years old) who met the Rotterdam criteria for PCOS were enrolled in the Gynaecology outpatient department at our hospital were included in the study. The subjects were categorised based on the Rotterdam criteria into 4 phenotype groups as phenotype-A (hyperandrogenism + ovulatory + polycystic ovarian morphology), phenotype-B (hyperandrogenism + ovulatory), phenotype-C (hyperandrogenism + polycystic ovarian morphology), and phenotype-D (ovulatory + polycystic ovarian morphology). Informed written consent was obtained from all individual participants included in the study.

For all study participants, a thorough clinical history was taken, including information about menstruation (h/o of the onset and duration of symptoms, duration of cycles, amount of flow, and treatment received), acne, hair growth at abnormal sites like the chin, upper lip and breast, weight gain or loss, acanthosis nigricans, galactorrhea and thyroid , as well as general, systemic, and local examination. This was followed by a baseline clinical evaluation, during which the following variables were noted: Height In Cm, Weight In Kg,

BMI Kg/m2, Waist Circumference, Hip Circumference, Waist:Hip Ratio &Waist:Height Ratio.
During the proliferative phase, transabdominal ultrasound was performed to record the thickness of endometrium & presence or absence of polycystic ovarian morphology.
Fasting total cholesterol, HDL cholesterol, non HDL cholesterol, computed Low density lipoprotein (LDL) cholesterol, and serum TGs were measured in order to analyse the lipid profile and also blood glucose levels (fasting & postprandial), HBA1C levels, Free testosterone levels & sex hormone binding globulin (SHBG) of all patients was estimated. Using the anthropometric & the biochemical parameters the following insulin resistance indices are calculated.

1. Visceral adipocity index (VAI) was calculated using the formula,

- Female VAI : $\left[\frac{WC\ (cm)}{\{36.58+(1.89x\text{BMI}(\frac{kg}{m^2}))\}}\right]$ x $\left[\frac{\text{TG(mmol/l)}}{0.81}\right]$ x $\left[\frac{1.52}{\text{HDL(mmol/l)}}\right]$

VAI: Visceral Adipose Index, WC: Waist Circumference, BMI: Body Mass Index, TG: Triglyceride, HDL: High Density Lipoprotein

(15)

2. Lipid Accumulation Product (LAP) was calculated using the formula, LAP = [WC (cm) – 58) x TG (mmol/L)]. (16)
3. triglyceride-glucose (TyG) index was calculated as: ln [fasting TG (mg/dL) × fasting plasma glucose (mg/dL)/2] . (17)
4. Single Point Insulin Sensitivity Estimator (SPISE) was calculated using the formula,

SPISE index = 600 × HDL- Cholesterol $[mg/dL]^{0.185}$/TG $[mg/dL]^{0.2}$/BMI $[kg/m^2]^{1.338}$ (18).

5. Free Androgen Index (FAI) was calculated using the formula,
   FAI= Total Testosterone (nmol/ L)) x 100 / Sex Hormone-Binding Globulin (SHBG) (nmol/ L) (19)

Statistical analysis:
The data was analyzed by Pearson's correlation coefficient for relationship between variables. Statistical analyses were performed with the help of SPSS software. For all statistical analyses the p value was considered to be significant when $p < 0.05$.

RESULTS:
In the present study, Forty women who met the Rotterdam criteria for PCOS were analysed. Among the 40 subjects, phenotype-A were 24, phenotype-B were 4, phenotype-C were 7 & phenotype-D were 5. TABLE:1 shows the descriptive statistics of age, anthropometrics, biochemical measures & insulin resistance indices in PCOS phenotypes.

TABLE:1 DESCRIPTIVE STATISTICS OF AGE, ANTHROPOMETRICS, BIOCHEMICAL MEASURES & INSULIN RESISTANCE INDICES IN PCOS PHENOTYPES.

PARAMETERS	PCOS-PHENOTYPES			
	PHENOTYPE – A N=24	PHENOTYPE – B N=4	PHENOTYPE – C N=7	PHENOTYPE – D N=5

	MEAN	STD. DEV	MEAN	STD. DEV	MEAN	STD. DEV	MEAN	STD. DEV
AGE	25.67	3.64	29.75	2.22	26.14	4.34	24.00	1.87
HEIGHT IN CM	158.75	7.01	151.25	2.75	157.71	9.34	156.00	1.58
WEIGHT IN KG	69.21	2.26	69.75	0.96	67.93	4.13	65.50	3.35
BMI KG/M2	27.61	2.50	30.52	1.44	27.45	2.50	26.92	1.49
WAIST CIRCUMFERENCE	71.71	9.02	67.75	2.06	69.86	5.37	71.00	9.38
HIP CIRCUMFERENCE	89.15	10.80	81.88	4.80	83.21	7.28	84.40	10.45
WAIST:HIP RATIO	0.81	0.06	0.83	0.03	0.84	0.03	0.84	0.03
WAIST:HEIGHT RATIO	0.45	0.06	0.45	0.02	0.44	0.04	0.46	0.06
FASTING BLOOD SUGAR(70-110mg/dl)	101.38	7.00	98.75	9.43	99.86	7.08	101.20	5.89
POST PRANDIAL BLOOD SUGAR (100-140mg/dl)	126.46	8.81	121.00	9.90	119.43	10.50	121.80	8.26
HBA1C (<5.7%)	4.69	0.56	4.98	0.33	4.64	0.59	4.38	0.55
T.CHOLESTEROL (150-220mg/dl)	173.08	15.40	170.00	9.63	180.29	15.50	162.40	16.13
HDL CHOLESTEROL(42-88mg/dl)	60.38	15.70	66.25	21.99	64.57	12.80	61.00	11.14
LDL CHOLESTEROL(<135mg/dl)	120.71	9.43	121.25	3.10	123.00	7.07	109.60	6.35

VLDL CHOLESTEROL(10-35mg/dl)	23.00	8.02	20.25	9.74	18.57	7.14	13.40	2.97
TRIGLYCERIDES (40-140mg/dl)	123.46	46.62	98.75	8.54	102.00	28.28	108.40	35.40
FREE TESTOSTERONE(15-70ng/dl)	68.71	4.00	70.05	2.16	70.97	3.72	47.40	6.11
SHBG (18-144nmol/L)	30.15	8.59	26.63	11.58	26.14	3.74	71.50	15.07
ENDOMETRIAL THICKNESS(mm)	5.42	1.06	3.90	0.48	6.23	0.98	5.21	1.29
VAI	3.53	2.32	2.31	1.24	2.35	0.55	2.85	1.33
LAP	105.72	97.66	53.33	11.26	70.32	41.69	85.40	77.80
FAI	8.61	2.72	10.33	3.81	9.61	1.57	2.40	0.63
TyG	8.68	0.36	8.49	0.15	8.50	0.31	8.57	0.30
SPISE	5.91	0.96	5.36	0.68	6.20	0.72	6.22	0.77

Table:2 shows the correlation between insulin resistance indices with endometrial thickness in phenotypes of PCOS.

TABLE:2 CORRELATION BETWEEN INSULIN RESISTANCE INDICES WITH ENDOMETRIAL THICKNESS IN PHENOTYPES OF PCOS.

PCOS PHENOTYPES	CORRELATION	VAI	LAP	FAI	TyG	SPISE
PHENOTYPE – A N=24	ENDOMETRIAL THICKNESS (mm)	0.11	0.05	0.17	-0.03	0.29
	P value (p < .05)	0.60	0.81	0.42	0.88	0.16
PHENOTYPE-B N=4	ENDOMETRIAL THICKNESS (mm)	-0.99	-0.59	0.94	-0.98	0.88
	P value (p < .05)	0.01	0.41	0.06	0.02	0.12
PHENOTYPE-C N=7	ENDOMETRIAL THICKNESS (mm)	-0.24	-0.02	0.56	-0.42	-0.52
	P value (p < .05)	0.60	0.96	0.19	0.34	0.23
PHENOTYPE-D N=5	ENDOMETRIAL THICKNESS (mm)	0.63	0.73	0.49	0.75	-0.62
	P value	0.25	0.16	0.40	0.14	0.26

	($p < .05$)					

Correlation between endometrial thickness & insulin resistance indices in PCOS Phenotype A, phenotype -C & phenotype-D samples: The indices VAI, LAP, FAI, TyG& SPISE showed negative correlation with endometrial thickness. In PCOS Phenotype B samples: The indices LAP, FAI & SPISE showed negative correlation whereas the indices VAI &TyG showed positive correlation with endometrial thickness with the Pearson's correlation coefficient value(R) of -0.99 with p value of <0.01 & value(R) of -0.98 p value of <0.02 respectively showing statistically significant.
Among the estimated insulin resistance indices VAI, LAP, FAI, TyG& SPISE, in the PCOS samples VAI &TyG showed positive correlation with endometrial thickness whereas the other indices like LAP, FAI & SPISE showed negative correlation. (FIG 01-05).

FIGURE:01 CORRELATION BETWEEN VAI & ENDOMETRIAL THICKNESS IN PCOS.

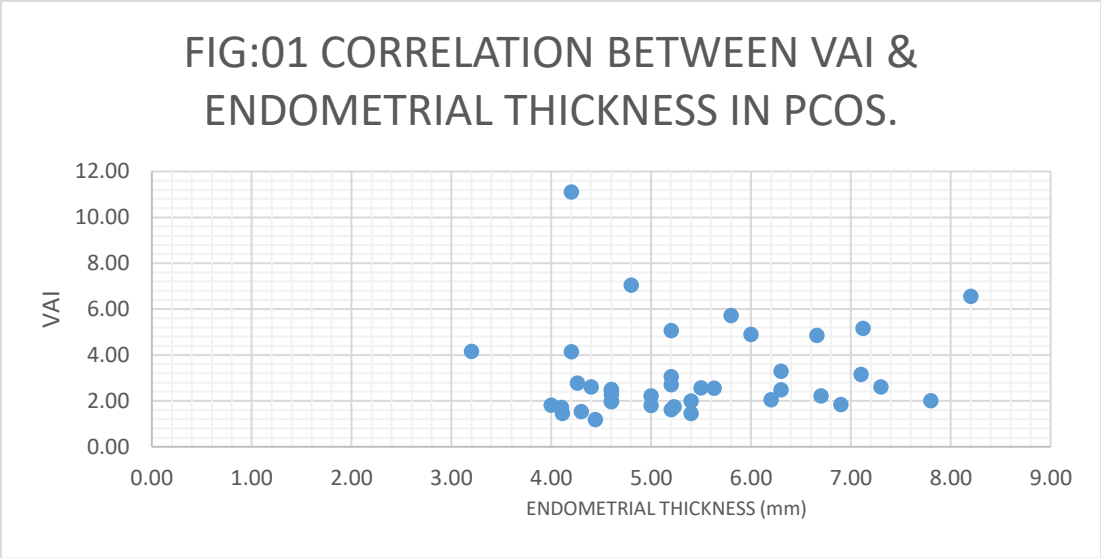


FIGURE:02 CORRELATION BETWEEN LAP & ENDOMETRIAL THICKNESS IN PCOS.

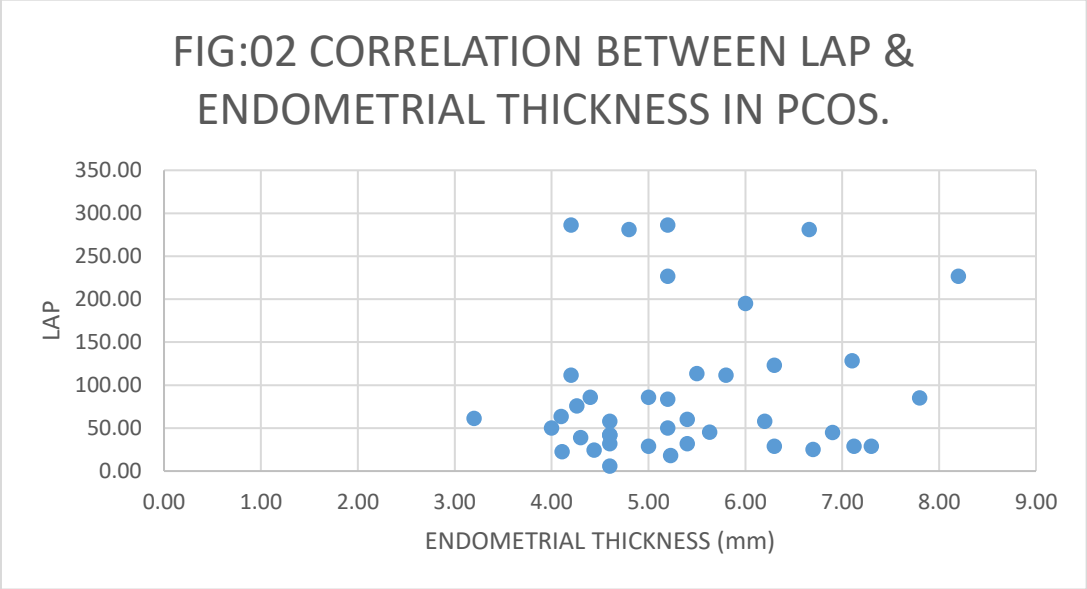


FIGURE:03 CORRELATION BETWEEN FAI & ENDOMETRIAL THICKNESS IN PCOS.

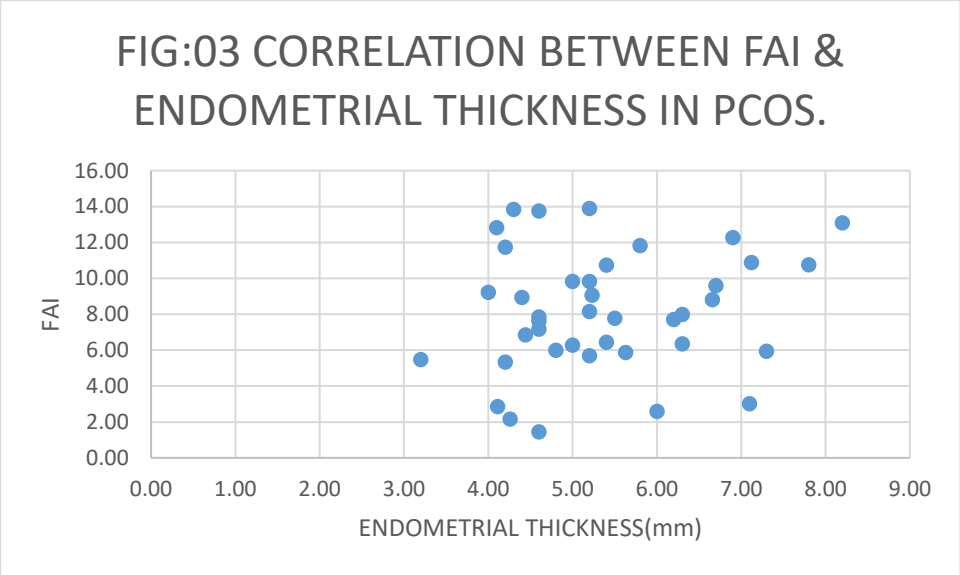


FIGURE:04 CORRELATION BETWEEN TyG& ENDOMETRIAL THICKNESS IN PCOS.

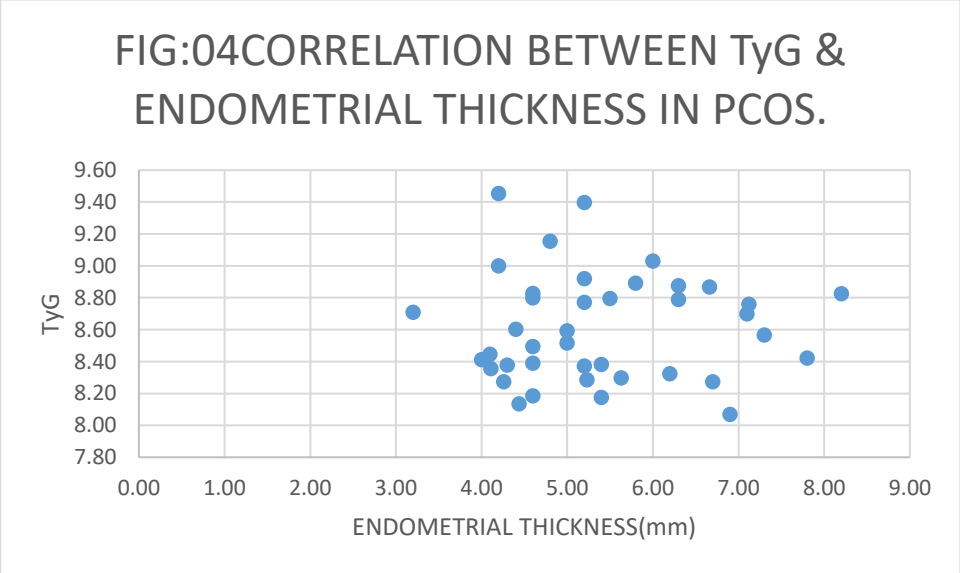
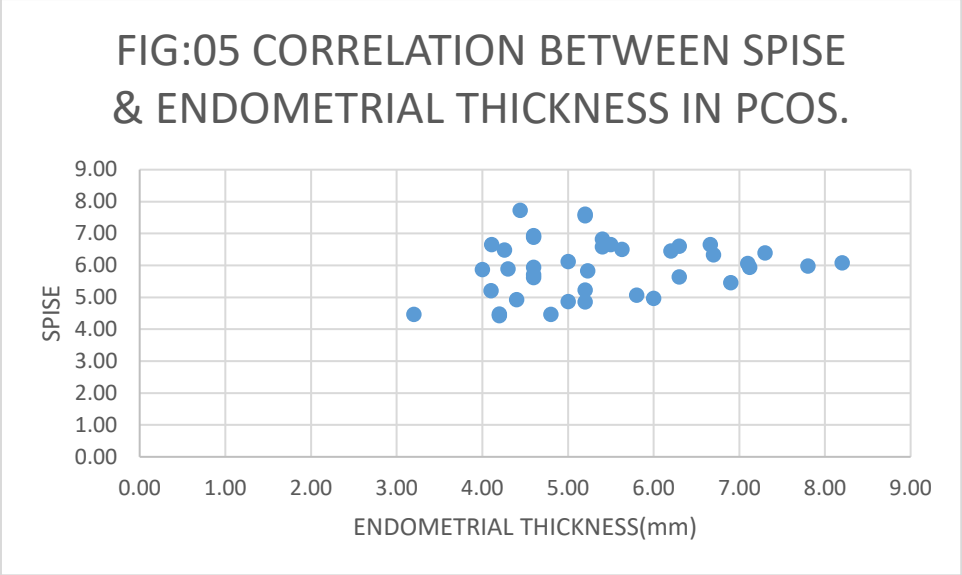


FIGURE:05 CORRELATION BETWEEN SPISE & ENDOMETRIAL THICKNESS IN PCOS.



DISCUSSION:

Obesity, Insulin resistance and dyslipidaemia are fundamental features of Metabolic syndrome (MS). No matter their BMI, PCOS individuals frequently have lipid abnormalities. Even though the risk for Metabolic syndrome and cardiovascular disease(CVD) is higher in PCOS patients, the present method for evaluating this risk is still not ideal. Finding a reasonably priced MS predictor would make it much easier to estimate MS, CVD &Ovulatory risk in PCOS. Hyperandrogenism, dyslipidaemia, and other metabolic abnormalities are more prevalent in MS-PCOS women (20). Our study aimed to identify & correlate simple and cost-effective tools for assessing the risk of MS, CVD & Ovulatory in phenotypes of PCOS.

VAI assessment considers both physical and metabolic parameters, VAI revealed a strong correlation with all MS variables. Also, VAI indirectly identifies other risk variables that aren't detected by BMI, WC, triglycerides, and HDL parameters alone, such as enhanced lipolysis, altered adipocytokine production, and plasma free fatty acids (21). The results of this study are consistent with those of Liu et al., who found a substantial direct connection between VAI and dysglycemia (22).

An insulin-free surrogate for determining insulin resistance has been sought for and developed due to the high cost and unavailability of insulin testing in the majority of laboratories in underdeveloped nations. The TyG index, which utilises fasting glucose and triglyceride levels, has recently been suggested as a helpful indicator for insulin resistance (23). Also studies have shown that cause of IR appears to be visceral fat accumulation, which is characterised by high lipolytic activity, and the TyG index is a useful indicator of visceral fat accumulation (24).

Recently, some studies have suggested that LAP which reflects lipid toxicity could be a sign of type 2 diabetes, IR, MetS, and non-alcoholic fatty liver disease (NAFLD) among the general population and could be linked to a higher risk of heart disease (25,26).

FAI was first developed in the early 1980s to evaluate hirsutistic females' testosterone levels. Also, Mendelian randomization study supports a causal role of SHBG in insulin and glucose metabolism & on the contrary, prediabetic hyperinsulinemia is thought to decrease SHBG production (27).

The Single-Point Insulin Sensitivity Estimator (SPISE) is a relatively simple mathematical method for estimating insulin sensitivity based on routine clinical measurements and labs such as BMI, triglycerides (TG), and HDL cholesterol. In few studies, SPISE showed good clinical performance in diagnosing MetS, T2DM, and coronary heart disease in adults and the elderly subjects (28,29,30).

Patients with Polycystic Ovary Syndrome (PCOS) experience chronic anovulation, which is characterized by an excessive amount of androgen or a deficiency of progesterone over

an extended period of time. This leads to an atypical form of endometrial hyperplasia, a condition that is a precursor to endometrial cancer. Risk of obesity and chronic metabolic disease resulting in decreased endometrial receptivity, which further leads to infertility, decreased implantation rate, increased abortion rate, and decreased live birth rate. Endometrial illnesses and endometrial cancer risk can be increased by metabolic disorders (31, 32). In particular, hyperinsulinemia raises the risk of developing endometrial cancer (33). Patients with metabolic syndrome usually have higher than normal amounts of estrogen, testosterone, and insulin (34)

An insulin-free surrogate for determining insulin resistance has been sought for and developed due to the high cost and unavailability of insulin testing in most laboratories in underdeveloped nations. The various insulin resistance indices used in the current study, which uses the regular biochemical parameters for estimating the insulin resistance can be helpful in identifying insulin resistance & predicting metabolic syndrome at the earliest. Also, the correlation between endometrial characteristics with insulin resistance can be effective in correcting ovulatory disfunction & metabolic syndrome in PCOS.

CONCLUSION:

In PCOS phenotypes, especially with PCOS Phenotype B there is a substantial correlation between the insulin resistance indices & endometrial thickness. They are simple and affordable markers that have a good sensitivity and specificity for the diagnosis of metabolic syndrome & ovulatory . By identifying metabolic syndrome & ovulatory early, lifestyle changes including dietary adjustments and regular exercise can be implemented at a young age to prevent the future development of type 2 diabetes mellitus and CVD. The reported results need to be corroborated by additional prospective studies with a bigger sample size.

Availability of data and materials

All data supporting the findings of this study are available within the paper.

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Contributions

Lavanya S collected patients' samples, clinical data & prepared samples for laboratory investigations, wrote the paper, did Statistical analysis, interpretation of data, and preparation of the paper for submitting. Critical revision of the manuscript was performed by Dr. Sureka Varalakshmi V.

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