A Dissertation On

EVALUATION OF EFFECT OF YOGANIDRA ON BIOCHEMICAL CHANGES IN POLYCYSTIC OVARIAN SYNDROME WOMEN BETWEEN THE AGE OF 18 - 35 YEARS

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The Institutional Ethics Committee of Government Yoga and Naturopathy Medical College, reviewed and discussed your application for approval of the proposal "EVALUATION OF EFFECT OF YOGANIDRA ON BIOCHEMICAL CHANGES IN POLYCYSTIC OVARIAN SYNDROME WOMEN BETWEEN THE AGE OF 18 - 35 YEARS" No. 12052016

The following members of Ethics Committee were present in the meeting held on 17/05/2016 conducted at Government Yoga and Naturopathy Medical College, Chennai.

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We approve the proposal to be conducted in its presented form

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The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patient's information / informed consent and asks to be provided a copy of the final report.

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LIST OF ABBREVIATIONS USED

(In Alphabetical Orders)

ASRM	American Society for Reproductive Medicine
BMI	Body mass Index
CBG	Corticosteroid-Binding Globulin
CRF	C reactive protein
CRH	Corticotrophin Releasing Hormone
CRP	C - reactive protein
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DHEAS	Dehydroepiandrosterone
DM	Diabetes Mellitus
DBP	Diastolic Blood Pressure
ESHRE	European Society for Human Reproduction and Embryology
FBS	Fasting Blood Sugar

F-G score	Ferriman -Gallwey (F-G) score
FSH	Follicle Stimulating Hormone
GnRH	Gonadotropin-releasing hormone
HbA1c	Glycated hemoglobin
HPA	Hypothalamic Pituitary Adrenal Axis
HDL	High Density Lipo Protein
IGF	Insulin Like Growth factor
IGT	Impaired glucose tolerence
IR	Insulin resistance
IGFBP-1	Insulin-like growth factor binding protein-1
IRS1-PI3KPKB	Insulin receptor substrate 1-phosphatidyl inositol 3 kinaseprotein kinase B
LDL	Low Density Lipoproteins levels.
LH	Luteinizing Hormone
MetS	Metabolic Syndrome
NIH	National Institutes of Health (NIH)

OS	Oxidative Stress
PAI-1	Plasminogen Activator Inhibitor Antigen
PPBS	Post Prandial Blood Sugar
PCOS	Polycystic ovarian syndrome
PSS	Perceived Stress Scale
PNS	Parasympathetic nervous system
SBP	Systolic Blood Pressure
SHBG	Sex Hormone Binding Globulin
SNS	Sympathetic Nervous System
TNF-α	Tumour Necrosis Factor - α
TG	Triglycerides
TSH	Thyroid Stimulating Hormone
UFC	Urinary Free-Cortisol
VLDL	Very Low Density Lipo Protein
WHR	Waist Hip Ratio

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

PCOS (Polycystic ovarian syndrome), a complex syndrome with endocrine and metabolic disorder of chronic anovulation, polycystic ovaries and biochemical and clinical manifestations of hyperandrogenism. Hypothalamic - pituitary adrenal axis impairment, impaired insulin secretion and action, and ovarian dysfunction are the defects involved in pathophysiology of PCOS leads to a metabolic syndrome culminating in serious long-term consequences such as type 2 diabetes mellitus, endometrial hyperplasia and cardiovascular diseases.

OBJECTIVE

An objective of the study is to evaluate the effect of YogaNidra on biochemical changes in Polycystic ovarian syndrome women between the age of 18-35 years.

METHODS

This study was conducted on 40 adult women between the age of 18-35 years not under any medication and fulfilling the Rotterdam criteria and inclusion criteria of this study. The study design is experimental pre post, YogaNidra practiced for 40 minutes 6 days a week up to 90 days; parameters were recorded at the baseline and also at the end of the study.

RESULT

Results of this study showed that a significant reduction ($P < 0.001$) in FBS and PPBS and significant reduction ($P < 0.0001$) in HbA1C, GTT.There was a significant reduction ($P < 0.001$) in cholesterol and triglyceride while a significant reduction ($p < 0.001$) seen among HDL, LDL, VLDL and on the anthropometric measurements significant reduction were seen in BMI($p < 0.001$), Weight ($p < 0.001$) and WHR ($p < 0.02$).

SBP and DBP showed a significant reduction $P < 0.0001$) after YogaNidra reveals the parasympathetic domination over sympathetic nervous system.

CONCLUSION

The present study demonstrated the efficacy of YogaNidra on biochemical profiles of PCOS women as an effective non pharmacological intervention in addressing the psychological and physiological concern of PCOS.

Key words: YogaNidra, PCOS, Biochemical Changes, HPA Axis, Stress

1. INTRODUCTION

Polycystic ovarian syndrome is a highly prevalent hormonal and metabolic disorder which affects 6-8 % **(Azziz, R et al., 2005)** globally prevalence estimates of PCOS are highly variable, ranging from 2.2% to as high as 26%. **(Michelmore et al., 1999)**

PCOS has significant and diverse clinical implications including reproductive (anovulation, irregular menstrual cycle, infertility, hyperandrogenism and hirsutism), metabolic (insulin resistance, impaired glucosetolerance, type-2 Diabetes Mellitus (DM), Cardiovascular Disease (CVD),Psychological features anxiety, depression, worsened the quality of life. **(Teede et al., 2010)**

According to ESHRE / ASRM (European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine) consensus conference on PCOS held in Rotterdam in 2003, PCOS was defined as at least 2 out of three following abnormalities.

(a) Oligo and/or anovulation,

(b) Clinical and/or biochemical sign of hyperandrogenism (hirsutism and/or acne or increased androgens levels)

(c) Detection of polycystic ovaries by ultrasound and presence of 10 or more cyst of 2-10mm in diameter in each ovary and absence of other endocrine conditions such as thyroid disorder, Cushing's syndrome, congenital virilizing adrenal hyperplasia or hyperprolactinemia.**(Rotterdam ESHRE / ASRM - Sponsored PCOS Consensus Workshop Group, T.R.E.A., 2004. Revised 2003)**

PCOS pathophysiology involves primary defects in the hypothalamic–pituitary adrenal axis, insulin secretion and action, and ovarian function **(Diamanti-Kandarakis.E et al., 2006, Shannon.M and Wang.Y 2012)**

Stress is a 'stimulus to produce disequilibrium in the homeostasis of physiological systems' resulting from a variety of stressors. The neuroendocrine changes associated stress can interpret the signals into pathophysiological alterations. **(Sridhar GR and Madhu K 2002)**

The hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) are triggered as a response to a stressor leading to a cascade of physiological, behavioral, and psychological effects, primarily as a result of the release of cortisol and catecholamines (epinephrine and norepinephrine).

Due to repeated firing of the HPA axis and SNS, the system gets de-regulated, leading to diseases such as autoimmune disorders, obesity, diabetes, substance abuse, depression, and cardiovascular disease. **(Sterling P 2004, McEwen BS 2000)**

Stress leads to increased levels of hormones like glucagon, cortisol, growth hormone, catecholamines,Corticotrophin Releasing Hormone (CRH), prolactin, leptin, neuropeptideY resulting in hyperglycemia which leads to diabetes. Bjorntop postulated that stress plays a role in diabetogenesis through activation of sympathetic nervous system following stress and leads to a series of hormonal changes leading to obesity and hence diabetes. Psychosocial stress may trigger the onset of visceral obesity and metabolic syndrome.

Central android obesity and peripheral gynoid obesity is associated with differential regulation of HPA and also targets metabolically important tissues such as liver and visceral fat. Chronic psychological stress was correlated with prevalence of type 2 diabetes mellitus and with visceral adiposity. The numbers of stressful events were positively associated with the prevalence of newly diagnosed diabetes. **(Thangasami S.R.et al., 2015)**

The association between insulin resistance and reproductive abnormalities with clinical hyper-androgenism in a woman was first demonstrated by Achard and Thiers in the "diabetes of bearded woman." The link of PCOS with insulin resistance was subsequently established by clinical studies characterizing the profound insulin resistance in obese and lean PCOS patients. **(Diamanti-Kandarakis 2006)**

Proven that hyperinsulinemia aggravating ovarian production of androgen.Among PCOS women 70% would be of Insulin Resistance (IR) and 10% would be Diabetic. **(Freeman, R.Pand Rosenbloom, R., E.2010, Farrell.K. and Antoni.M.H 2010, Ovalle.F and Azziz, R 2002)**

PCOS is commonly associated with glucose metabolism abnormalities and is an independent risk factor for the development of diabetes.Impaired glucose tolerance, measured by oral glucose tolerance test, may approach 30–40% in obese populations with PCOS. **(Legro.R.S. et al., 1999, Ehrmann.D.A.et al., 1999)**

The association between PCOS and an increased rate of incident diabetes remained even in women with a BMI of less than 25. **(Wang 2011)**

IR with elevated circulating insulin levels induces unfavorable changes in the lipid metabolism and increased androgen production from the theca cells.Androgen excess may lead to dyslipidemia and central distribution of fat (android pattern).In obese women, excess insulin and androgens may contribute to the development of the PCOS and metabolic syndrome. **(Eckel.R.H. 2005)**

The android pattern of fat distribution could be the result and also the cause for hyperandrogenism, setting up a vicious circle of hyperinsulinism, hyperandrogenism, central adiposity and metabolic abnormalities. **(Barber.T.M et al., 2006)**

Modern neurophysiologists have been able to demonstrate an obvious relationship between the body and the brain which was first recognized by the ancient yogis thousands of years ago. Using stimulating electrodes to probe the brain surface, neurosurgeons have shown that each part of the body is precisely mapped out along the surface of the central gyrus or fold of the sensory motor cortex of the brain.

YogaNidra is a systemic method. YogaNidra was found and formulated by Swami Satyananda Saraswati of Bihar school of yoga. In yogic system, YogaNidra is considered as a form of rajayoga, YogaNidra belongs to the higher stages of raja yoga, since it is essentially a method of pratyahara - fifth stage of patanjali ashtanga yoga. **(Swami Satyananda Saraswati, Yoganidra 2001)**

Chapter four of Hatha Yoga Pradipika also speaks of YogaNidra. **(Swami. S.S. Hathayogapradipika, 1998)**

In Hatharathnavali, YogaNidra is said as an asana, where in the legs are wound around the neck and hands are tied on the back and lied down. This is said to improve the positive health. **(Srinivasa yogi, Hatharathnavali.2009)**

During the practice of YogaNidra one appears to be asleep but the consciousness is functioning at deeper level of awareness, more efficient and effective in therapeutic applications also in many disease conditions.YogaNidra is a systemic method of inducing complete physical, mental and emotional relaxation.YogaNidra practice was helpful in patients with hormonal imbalances such as dysmenorrhea, oligomenorrhea, menorrhagia, metrorrhagia and hypomenorrhea **(Rani.M et al., 2013,Rani.K 2016)** for diabetes – blood glucose level **(Amita.S et al., 2009)**, Stress, anxiety and depressive symptoms **(Singh.U et al., 2012, Rani.K et al., 2011, Rani.K et al.,2016)** and also cardio vascular diseases.

YogaNidra appears to regulate hypothalamus,in a way resulting in decreased sympathetic (excitatory) nervous activity and increased parasympathetic (inhibitory) function **(Satyananda.S. 2009)** there by YogaNidra reduces the stress **(Kumar.K 2008)**, oxidative stress, chronic inflammation, insulin resistance and it also reduce hyperinsulinaemia, increases SHBG thereby reducing the androgen level through regulating the hypothalamic pituitary ovarian axis regulate the SNS and hypothalamao pituitary adrenal axis, can prevent and reduce the consequences of PCOS also effective in treating the long term consequences of diabetes mellitus, cardiovascular diseases, and dyslipidemia.

Many studies available in yoga for PCOS as an effective management as a lifestyle modification and also a form of exercise, but there is a lacuna in effect of YogaNidra on PCOS patients. So the present study was planned to assess the effect of YogaNidra practice on biochemical changes in PCOS patients.

2. AIMS AND OBJECTIVES

Aim:

- To evaluate the effect of YogaNidra on Blood glucose level, Lipid profile, BMI, Waist Hip Ratio and Blood Pressure in Polycystic Ovarian syndrome women aged between 18-35 years.

Objectives:

Primary objective(s):

- To assess and compare blood glucose levels in PCOS before and after 12 weeks of YogaNidra
- To assess and compare lipid profile in PCOS before and after 12 weeks of YogaNidra

Secondary objective(s):

- To evaluate the changes in the Body Mass Index (BMI) before and after 12 weeks of YogaNidra
- To evaluate the changes in the Waist Hip Ratio (WHR) before and after 12 weeks of YogaNidra
- To evaluate the changes in the Blood Pressure (systolic and diastolic blood pressure) before and after 12weeks of YogaNidra.

3. REVIEW OF LITERATURE

3.1. POLYCYSTIC OVARIAN SYNDROME

Polycystic ovarian syndrome (PCOS) is a multifactorial, heterogeneous, complex genetic, endocrine and metabolic disorder, diagnostically characterized by chronic anovulation, polycystic ovaries and biochemical and clinical manifestations of hyperandrogenism. It has a tremendous negative impact on the physiology and metabolism of the body as it may evolve into a metabolic syndrome with insulin resistance, hyperinsulinemia, abdominal obesity, hypertension and dyslipidemia presenting as frequent metabolic traits and culminating in serious long-term consequences, such as type 2 diabetes mellitus, endometrial hyperplasia and cardiovascular disease. **(Diamanti Kandarakis 2006)**

PCOS has significant and diverse Clinical implications including

- **Reproductive (**anovulation,irregularmenstrualcycle,infertility, hyperandrogenism and hirsutism),
- **Metabolic** (insulin resistance, impaired glucose tolerance, type -2 Diabetes Mellitus (DM), Cardio vascular Disease (CVD),
- **Psychological features** (anxiety, depression, worsened the quality of life). **(Teede et al., 2010)**

3.1.1 CLINICAL FEATURES OF PCOS

PCOS is most simply defined as the presence of hyperandrogenism (clinically and/or biochemically) and/or chronic anovulation in the absence of specific adrenal and/or pituitary disease. **(Dunaif A 2001)**

Table 1. Clinical features of polycystic ovary syndromes
• Oligomenorrhea / amenorrhea
• Infertility/first trimester miscarriage
• Obesity
• Hirsutism
• Acne
• Acanthosis nigricans
• Male pattern alopecia

Table.1 Outlines the clinical features of PCOS.

Hyperandrogenism may present clinically as hirsutism, acne and / or male pattern alopecia.Hirsutism can be defined as the growth of coarse hair on a woman in a male pattern (upper lip, chin, chest, upper abdomen, back etc.).This is to be distinguished

from hypertrichosis that involves a more uniform, whole body distribution of fine hair. Acne related to hyperandrogenism may be difficult to distinguish from normal

pubertal acne in an adolescent with PCOS though pubertal acne in general is twice as prevalent in adolescent males versus females and males are more likely to have severe disease. **(Barth JH and Clark S 2003)**

The severity of any of these manifestations is highly variable and may depend on genetic and ethnic differences in the sensitivity to the effects of androgens. The presence of virilization (clitoromegaly, deepening voice, increased musculature, or rapidly progressive hirsutism or alopecia), however, is not a feature of PCOS, but instead of more severe hyperandrogenism.

Chronic anovulation often presents as oligomenorrhea, amenorrhea, dysfunctional uterine bleeding, and/or infertility. Interestingly however around 20% of patients with PCOS may describe normal menstrual cycles. **(Conway GS et al., 1989)**

Often, but not always, menstrual abnormalities are long-standing, even since menarche. Other women may only develop menstrual problems later in life, perhaps after significant weight gain. Furthermore, primary amenorrhea is possible although not common.

When clinically evaluating a patient for the possibility of PCOS, it is also important to search for signs of Insulin resistance (IR).Upper-body obesity is a key component of the IR syndrome.**(Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. (NCEP) (Adult Treatment Panel III) 2001)**

Obesity is not required for the diagnosis of PCOS with perhaps only 35% to 50% of these patients being obese **(Knochenhauer ES et al., 1998, Pasquali R et al., 1993)**

Acanthosis nigricans on physical examination is a sign of IR.A personal or family history of type 2 diabetes mellitus or gestational diabetes mellitus or the presence of hypertension should also be sought in the evaluation. The criteria for diagnosis of the Insulin resistance in women should be evaluated in all patients. (Table.2) (**De Groot LJ 2000)**

Table .2. Diagnostic criteria for the insulin resistance syndrome in women.	
Any three or more of the following:	
Waist circumference	MEN ≥ 102cm, WOMEN ≥ 88cm
Triglycerides	> 150 mg/dL
HDL-cholesterol	MEN < 40 mg/ dL, WOMEN < 50 mg/ dL
Blood pressure	≥ 130/85 mm
Fasting glucose	>100 mg/Dl

After PCOS is diagnosed, studies show that more than 50% of patients develop prediabetes or diabetes, and there is an increased risk of myocardial infarction (MI), dyslipidemia, hypertension, anxiety, depression, endometrial cancer, and sleep apnea. Moreover, pregnant women with PCOS should be informed of the increased rates of miscarriage, gestational diabetes, pre-eclampsia, and premature delivery **(Hurd.W.W et al., 2011)**

3.1.3. DIAGNOSTIC CRITERIA FOR PCOS

Diagnostic criteria for PCOS have been offered by three groups:

Table.3 Criteria for the diagnosis of polycystic ovary syndrome

NIH/NICHD 1992	ESHRE/ASRM (Rotterdam criteria) 2004	Androgen Excess Society 2006
Exclusion of other androgen excess or related disorders	Exclusion of other androgen excess or related disorders	Exclusion of other androgen excess or related disorders
Includes all of the following:	Includes two of the following:	Includes all of the following:
• Clinical and/or biochemical hyperandrogenism	• Clinical and/or biochemical hyperandrogenism	• Clinical and/or biochemical hyperandrogenism
• Menstrual dysfunction	•Oligo-ovulation or anovulation • Polycystic ovaries	• Ovarian dysfunction and/or polycystic ovaries

Abbreviations: ESHRE/ASRM, European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine; NIH/NICH, National Institutes of Health/National Institute of Child Health and Human Disease.

The National Institutes of Health/National Institute of Child Health and Human Disease (NIH/NICHD); **(Zawadski JK and Dunaif A 1992),**the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM); (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. (*Fertil Steril*. 2004) and the Androgen Excess and PCOS Society. **(Azziz R E et al. 2006)**.These criteria are summarized in Table 3.

3.1.4 INVESTIGATIONS AND ASSESSMENT IN PCOS

There is no single diagnostic test for PCOS. Key investigations include prolactin and thyroid stimulating hormone to exclude other disorders and testosterone, SHBG and free androgen index to assess androgen status. **(Norman RJ et al., 2007)**

Investigations include a pelvic ultrasound for ovarian morphology and endometrial thickness. An oral glucose tolerance test (rather than fasting glucose) and lipid profiles are appropriate in all women at diagnosis and 1 to 2 yearly after this, where women are overweight or have an increased risk of DM2 (for example, family history of DM 2 in first-degree relatives, increased age or high-risk ethnic group).As noted, insulin levels should not be measured in clinical practice because of assay variability and inaccuracy. Metabolic syndrome and abnormal glucose metabolism best reflect insulin resistance in this population. **(Teede *et al.*, 2010)**

3.2. PATHOPHYSIOLOGY OF PCOS

The pathophysiology of PCOS involves primary defects in the hypothalamic–pituitary axis, insulin secretion and action, and ovarian function. **(Diamanti-Kandarakis.E et al., 2006, Shannon.M and Wang.Y 2012)**

3.2.1 ROLE OF HYPOTHALAMIC PITUITARY ADRENAL AXIS (HPA) IN PCOS

Adrenal steroidogenesis is under the control of the hypothalamic - pituitary - adrenal (HPA) axis. Furthermore, metabolic factors including insulin and obesity-related signals may play a role in the regulation of both enzymes involved in the steroid genetic pathways, as well as in the regulation of the HPA axis.

In women with the polycystic ovary syndrome (PCOS), cortisol production rate is probably normal, although adrenal androgens can be overproduced in a subset of affected women.

Cortisol metabolism and regeneration from inactive glucocorticoids can also be disrupted in PCOS, thereby contributing to determining an adrenal hyperandrogenic state. Finally, over activity of the HPA axis may be related to the high prevalence of psychopathological and eating disorders in women with PCOS, implying a maladaptive allostatic load in the adaptive mechanisms to chronic stress exposure.

Metabolic abnormalities that may be very common in women with PCOS, particularly insulin resistance and obesity. Insulin is a true gonadotropic hormone that synergizes

with the luteinizing hormone (LH) in the regulation of ovarian steroidogenesis **(Nestler JE 2008)**

It may amplify ovarian androgen production rates, thereby representing a triggering factor in the pathogenesis of hyperandrogenism. **(Ehrmann DA 2005)**

In addition, insulin negatively regulates the synthesis of the major carrier protein of androgens, the sex-hormone-binding globulin, and therefore reduces circulating sex-hormone-binding globulin levels that, in turn, increase the availability of free testosterone in peripheral tissues and cells **(Ehrmann DA. 2005)**

Hyperandrogenism, in turn, contributes to the generation of insulin resistance through the stimulation of lipolysis, and therefore the increased blood availability of free fatty acids and the modification of muscle–skeletal structure and metabolic activity **(Pasquali R. 2006)**

Obesity may also play an important role in the pathophysiology of PCOS; therefore, obesity *per se* represents a condition of sex-hormone imbalance in women. In fact, testosterone production rate can be significantly increased whereas its metabolic clearance rate remains unchanged, and the availability of free testosterone may increase along with the production rate of estrogens **(Pasquali R 2006)**

In addition, the presence of obesity implies an important additional contribution in determining the insulin-resistant states and in increasing blood insulin concentrations **(Morales AJ et al., 1996)** Finally, lipid soluble steroids, including androgens, can be stored in the adipose tissue, where concentrations may be higher than in the blood,

thereby determining that the steroid pool in obese subjects is greater than that in normal-weight individuals. In addition, steroids are actively metabolized or interconverted in the adipose tissue, because of the presence of steroidogenenic enzymes, such as 3b-dehydrogenase, 17b-hydroxydehydrogenase and the aromatase system. Alterations in these metabolic pathways may contribute to increased androgen peripheral production rates in obese women with PCOS. In turn, androgens may also promote the differentiation of preadipocytes into mature adipocytes, particularly in the visceral fat. **(Pasquali R 2006)**

3.2.2. CORTISOL PRODUCTION & THE HYPOTHALAMIC – PITUITARY - ADRENAL AXIS IN PCOS

The glucocorticoid hormones - cortisol (in humans) and/or corticosterone (in animals) - are secreted in the adrenal glands under the control hypothalamic structures and the pituitary gland, which form the structural organization of the hypothalamic - pituitary - adrenal (HPA) axis.

In the hypothalamic areas, the cascade is in turn chiefly regulated by the corticotropin-releasing hormone (CRH) and arginine-vasopressin, **(Lightman SL 2008)** whose release activates pro-opiomelanocortin in anterior pituitary corticotroph cells and the release of ACTH into peripheral blood, from where it targets receptors in the adrenal cortex to release glucocorticoid hormones.

In the hypothalamus, the parvocellular cells of the paraventricular nucleus of the hypothalamus are the major information junction for the neuroendocrine response to both internal and external excitatory stimuli. **(Herman JP et al., 2003)**

There is a hierarchical organization of the responsive neurocircuitries upon the paraventricular nucleus, which is capable of integrating information from multiple limbic sources with internally generated and peripherally sensed information, thereby tuning the relative activity of the adrenal cortex. **(Herman JP et al., 2003)** These circuits are particularly involved in the response to physical and psychological stress, both acute and chronic. In most organisms the system efficiently modulates the HPA axis in accordance with needs; however, there is a considerable individual variation in the HPA response disposition and some influence of genetic factors and early-life experience. **(Herman JP et al., 2003)** Importantly, the organization of the HPA axis is under the control of sex hormones, thereby explaining some physiological and pathophysiological differences between the sexes in its regulation and activity. **(Viau V 2002, Williamson M et al., 2005)**

3.2.3. DYNAMIC TESTS ASSESSING THE ACTIVITY OF THE HPA AXIS IN PCOS

There are only a few studies that have investigated the functioning of the adrenals following neuropeptide administration or specific challenges able to evoke primary neurooendocrine over activation stimuli. Some evaluated the HPA axis response to ovine (oCRH) or human (hCRH) stimulation at different doses in PCOS.

Lanzone ***et al***. found that both ACTH and cortisol response to hCRH were markedly greater and more prolonged in women with PCOS as compared with controls. Later, the same group found that after 6 weeks of treatment with a somatostatin analog, octreotide treatment (100 mg subcutaneously, twice daily),

ACTH and cortisol response significantly decreased in women with PCOS, and no difference was present with respect to controls, suggesting that a hyperfunction of the HPA axis secondary to central and/or peripheral somatostatinergic activity in these women might exist. **(Lanzone A et al., 1997)**

Another study **(Azziz R et al., 1997)** investigated whether women with PCOS characterized by DHEAS excess differed, with respect to those with normal DHEAS blood values or controls (matched for age and BMI), in the response to oCRH stimulation (1 mcg/kg) or an 8-h incremental intravenous stimulation with ACTH (1–24) at doses ranging from 20 to 2880 ng/1.5 m^2 × h with a final bolus of 0.25 mg.

No significant differences in the net maximal response for ACTH, dehydroxyepiandrosterone (DHEA), androstenedione or cortisol were observed; nonetheless, the net response of the DHEA/cortisol ratio and of the areas under the curve for DHEA and the DHEA/cortisol ratio indicated a greater response for PCOS women with high DHEAS levels compared with both their counterparts. Moreover, no difference in the sensitivity (i.e., threshold or minimal stimulatory dose) to ACTH was noted between the groups for any of the steroids measured; however, the average dose of ACTH (1–24) required for a threshold response was higher for DHEA than for cortisol and androstenedione in all groups. In addition, no difference in mean responsivity (slope of response to incremental ACTH stimulation) was observed for DHEA and cortisol between the study groups, whereas the responsivity of androstenedione was higher in PCOS women with high DHEAS than in those with normal DHEAS. Collectively, the data of this complex study seem to support the concept that adrenal androgen excess in PCOS patients is related to an exaggerated

secretory response of the adrenal cortex (for DHEA and androstenedione), but not to an altered pituitary responsivity to CRH or to increased sensitivity of these androgens to ACTH stimulation. However, the data could not define whether the increased responsivity to ACTH for these steroids might be secondary to increased zona reticularis mass or to differences in P450c17a activity, particularly of the delta-4 pathway.

In this regard, an interesting study **(Wu XK et al., 2000)** has suggested that, in women with PCOS, ovarian hyperandrogenicity may potentially directly contribute to the enhanced adrenal P450c17a activity and subsequent delta-4 androgen reserve revealed by ACTH (1–24) stimulation, independently of mechanisms regulating adrenal cortisol secretion. Intriguingly, this might imply a functional crosstalk between the ovaries and the adrenals. A third study evaluating the dynamics of the pituitary–adrenal hormone response to hCRH in women with PCOS, Kondoh ***et/al***. found that plasma ACTH and cortisol response were significantly higher with respect to controls only in a subgroup of women with PCOS, and that these women were also characterized by higher blood levels of DHEAS, but greater suppression of androstenedione following dexamethasone administration. **(Kondoh et al., 1999)**

Mechanisms responsible for an increased responsiveness of the HPA axis - which can be detected only in specific subsets of women with PCOS - are still unclear, although altered somatostatinergic **(Lanzone A et al., 1997)** and opioid system **(Fulghesu AM et al., 1998, Lanzone A et al.,1996)** functions, possibly contributing to a hyperactive HPA axis have been suggested.

Finally, one study investigated the HPA response to insulin-induced hypoglycemia in a small group of women with PCOS and weight-matched controls **(Gennarelli G et al., 1999)**. It was found that, compared with controls; women with PCOS had a significantly lower ACTH response, and a quantitatively comparable and more prompt cortisol response than the controls, resulting in a higher molar ratio between the maximum increments of cortisol and ACTH. Furthermore, a more rapid decline in cortisol levels occurs in PCOS than the controls, where as the responses of the androgens and intermediate adrenal steroids were similar in both PCOS and control women. The findings may suggest an adaptation to increased adrenal reactivity to endogenous ACTH in women with PCOS, although this model, used to investigate neuroendocrine reactivity, did not show hypersecretion of adrenal androgens and revealed no signs of steroid enzyme disturbances. Questions of the extent with differences in enzyme activities in the cortisol metabolism contribute to the rise in production remain unresolved because a quantitative kinetic model of cortisol metabolism is not available.Therefore, understanding the mechanisms responsible for altered cortisol and eventually adrenal androgens after stimulatory challenges is still a difficult task.In line with these findings, a potential indirect role of nutrients and insulin in the regulation of adrenal steroidogenesis has also been suggested by a recent study showing that, in women with PCOS, the presence of obesity and insulin resistance is associated with lower morning cortisol and DHEAS but increased cortisol and DHEA responses during an oral glucose tolerance test. Specifically, those women who had higher BMI and lower insulin sensitivity indices also had a higher early (at 60 min) response to glucose load and a later lower late nadir (at 180–240

min) glucose values. These nadir values were significantly associated with late cortisol increase and with higher scores in shakiness, sweatiness, weakness and hunger, suggesting the presence of reactive hypoglycemia in these women and, therefore, explaining the reactive cortisol increase. **(Gurusinghe D et al., 2010)**

Interestingly, this hormonal imbalance in obese insulin resistant and hyperinsulinemic patients with PCOS might have important long-term consequences because of repeated stimulation of the HPA axis by nutrients. In fact, it is conceivable that ingestion of simple sugars can cause even mild postprandial hypoglycemia, thereby stimulating secretion of adrenal steroids that, in turn, may favor further weight gain and insulin resistance, thus creating a vicious cycle.

To summarize, all available studies support the possibility that the HPA axis response to neuroendocrine stimuli may be altered only in a subset of women with PCOS, in whom metabolic factors, such as obesity and insulin excess, may play a role in determining abnormalities in the regulation of the adrenal axis.

3.2.4. THE ROLE OF OBESITY IN MODULATING THE ACTIVITY OF THE HPA AXIS IN PCOS

Obesity represents a potential factor responsible for altered HPA axis functioning in PCOS, and this may be supported by the strong association between these two disorders and by the fact that the pulsatile and spiky activity of ACTH secretion are under the influence of body fat and body composition, as well as age. **(Veldhuis JD et al., 2009)** this may be due to the fact that these confounders were not adequately taken into account. In fact, several studies performed in women with different phenotypes of

obesity have shown that a dysregulation of the HPA axis may exist in this population, particularly those with the abdominal phenotype. **(Pasquali R et al., 2008)**

In these women, basal blood levels of ACTH and cortisol are usually normal, as are ACTH and cortisol daily rhythms. **(Chalew S et al., 1995)**

However, one study performed to investigate the pulsatile secretion of cortisol and ACTH during the daytime in women with different obesity phenotypes showed that those with visceral obesity had higher ACTH pulse frequency and lower ACTH pulse amplitude, particularly in the morning, but similar mean ACTH basal concentrations, in comparison with their gluteofemoral type obese counterpart and normal-weight controls, **(Pasquali R et al., 1998)** suggesting an increased sensitivity of cortisol secretion to non-ACTH-dependent pathways, such as the peripheral noradrenergic regulatory system, particularly during the zenith phase of the daily rhythm. Several other studies used the urinary free-cortisol (UFC) excretion as an integrated measurement of daily cortisol excretion rate, and reported higher than normal 24-h UFC excretion rates in women with abdominal obesity, and a significant positive correlation with the extent of abdominal adiposity. **(Pasquali R et al., 1993, Duclos M et al., 1999, Epel EE et al., 1999)**

Dynamic studies in which the HPA axis was either stimulated or inhibited provided the most convincing evidence for a dysregulation of the system in abdominal obesity. They demonstrated higher than normal cortisol responses after laboratory stress tests, or after challenges of the HPA axis by administering CRH or arginine-vasopressin alone, or in combination **(Pasquali R et al., 2006)**, in women with abdominal obesity

with respect to those with the peripheral phenotype, even regardless of psychiatric disorders. **(Vicennati V et al., 2000)**

The strong reproducibility of the CRH test among individuals is undoubtedly a strength factor supporting the reliability of these data. **(Bertagna X et al., 1994)** Similar differences between abdominal and peripheral obese women have been reported by using the ACTH (1–24) stimulatory test, using either maximal or low doses**. (Pasquali R et al., 1993)**

The suppressive challenge of the HPA axis using low-dose (i.e., ≤0.5 mg overnight) dexamethasone provided relatively confirmatory results. A blunted inhibition of cortisol secretion, suggesting a reduced sensitivity to inhibition by low-dose dexamethasone via downregulation of central glucocorticoid receptors, has been reported. **(Ljung T et al., 1996)**

Another study, in both obese and normal-weight individuals who randomly underwent different low-dose dexamethasone doses showed that, unlike men, with increasing amounts of abdominal fat, women tended to show a significant lower suppression of blood cortisol levels with respect to that expected on the basis of increasing dexamethasone doses) **(Pasquali R et al., 2002**) further confirming the potential impairment of sensitive feedback signals in abdominally obese women.

The data showed that basal, pulsatile and total cortisol production (expressed per liter of distribution volume, per square meter of body surface and as absolute amount per 24-h) was similar in PCOS patients and matched healthy controls. Accordingly, the regularity of cortisol secretion and the diurnal properties or circadian rhythm were

identical. However, compared with ten lean control women, mean cortisol production per liter of distribution volume was similar in the three groups, but the total 24-hr cortisol production was increased in obese control women and PCOS women. These data confirm previous studies investigating cortisol secretion in obesity assessed with different methods, including isotopic dilution, measurement of UFC and C21 metabolites that have invariably shown increased cortisol production in obesity**. (Dunkelman SS et al., 1964, Strain GW et al., 1980, Stewart PM et al., 1999, Roelfsema F et al., 2009)**

3.2.5. THE ROLE OF INSULIN ON ADRENAL STEROIDOGENESIS

Insulin is able to regulate gonadal steroidogenesis in both males **(Pasquali R et al., 1995**) and females. **(Poretsky L et al., 1994)** In women with PCOS, insulin excess amplifies ovarian androgen production rates**, (Dunaif A et al., 1989)** independent of changes in gonadotropin secretion and activity. Although earlier studies produced conflicting results, **(Nestler JE et al., 1987, Stuart CA et al., 1987)** a study performed in PCOS women and healthy controls, where LH responses to varying doses of gonadotropin releasing hormone (GnRH) during a fixed rate of insulin infusion and LH responses to a fixed dose of GnRH during varying doses of insulin infusion were investigated, showed that in the latter both basal LH and LH responses to GnRH were unaltered by insulin infusion, whereas these measures were reduced during insulin infusion in women with PCOS, and that this effect was negatively dependent on body weight**. (Lawson MA et al., 2008)**

The role of insulin and other factors, particularly IGFs 1 and 2, in the regulation of ovarian theca and granulosa cells has been repeatedly demonstrated by ***in vitro*** studies performed in animal models and human tissues.

These studies provided the basis for the role of insulin excess in determining increased androgen production and enhanced follicular cyst development in the PCOS. **(Poretsky L et al., 1999)**

The key enzyme system representing the target of insulin action in the ovaries is cytochrome P450c17α, as shown by the increased activity of 17α-hydroxylase and, to a lesser extent, of 17, 20-lyase, resulting in excessive ovarian androgen production. **(Nestler JE 2008)**

A more recent study further supported that sustained hyperinsulinemia is capable of potentiating gonadotropin-stimulated ovarian androgen steroidogenesis in women with PCOS.**(Tosi F et al., 2012)**More recent studies provided ***in vivo*** data demonstrating that, in women with PCOS, a steady state of insulin excess produced proof of the concept that hyperinsulinemia is associated with an amplification of the 17α-hydroxycorticosteroid intermediate response to ACTH stimulation, without alterations in serum cortisol or androgen response to stimulation.

This was demonstrated by evaluating the adrenal steroid response to ACTH (1–24) or saline infusion during a 3-h hyperinsulinemic (80 $mU/m^2 \times min$) euglycemic clamp in a group of 21 hyperandrogenic women with PCOS. **(Moghetti P et al., 1996)**.It was found that no significant difference in the cortisol, progesterone or androstenedione response to ACTH was present between the ACTH and the saline

infusion. By contrast, ACTH-stimulated serum 17-hydroxypregnenolone ($p < 0.005$) and 17-hydroxyprogestrone ($p < 0.01$) were significantly higher during insulin than during saline infusion, with a modest but significant increase in serum DHEA during hyperinsulinemia.Inaddition, ACTH-stimulated 17 - hydroxypregnenolone /DHEA($p<0.001$)and17b-ydroxyprogestrone/androstenedione ($p < 0.005$) molar ratios, indexes of apparent 17, 20-lyase activity, were significantly higher during the clamp studies than during saline infusion. These ***in vivo*** data therefore support the hypothesis that insulin potentiates ACTH-stimulated steroidogenesis, and that this effect of insulin is probably to be associated with a relative impairment of 17, 20-lyase activity. In a more recent study, the same research group provided further evidence for the presence of an insulin-mediated dysregulation of adrenal steroidogenesis. **(Tosi F et al., 2011)**

These findings demonstrate that the decrease of circulating insulin may improve adrenal steroidogenesis, possibly through a regulation of peripheral cortisol metabolism, rather than affecting cortisol production rate from the adrenals. By contrast, studies with metformin have produced disparate results, showing changes in the circulating hormones compatible with a significant decrease in the activity of 3b-hydroxysteroid dehydrogenase in C **(Gennarelli G et al., 1999)** steroids and in 17b-hydroxysteroid dehydrogenase after ACTH stimulation in one study, or unaltered 17b-hydroxyprogesterone and androstenedione responses to ACTH (1–24) stimulation in another study suggesting no direct relationship between insulin resistance and adrenal P450c17a enzyme dysregulation**.(Unlühizarci K et al., 1999)**

3.2.6. CORTISOL & THE HPA AXIS ACTIVITY & THEIR RELATIONSHIP TO STRESS & EATING BEHAVIOR : IMPLICATIONS FOR THE PATHOPHYSIOLOGY OF PCOS

PCOS is associated with several psychological disturbances and reduced quality of life **(Benson S et al., 2009)** This may reflect the individual discomfort to the presence of signs (i.e., hirsutism) and symptoms (i.e., irregular menstruations). Obesity itself may have a significant psychopathological impact, and may lead to poorer psychological heath by producing body dissatisfaction and lower self esteem. **(Hill AJ et al., 1998, Johnson F et al., 2005)**

Collectively, these traits may lead to perceived chronic stress and subsequent maladaptive response, which per se may play some role in the pathophysiology and the development of metabolic alterations often associated with PCOS, and the subsequent susceptibility to develop metabolic and cardiovascular diseases.

A specific phenotype of obesity related to poor coping to a stressful event, which is characterized by rapid weight gain and increased daily UFC excretion rates.**(Vicennati V et al., 2009)**

Given the very high prevalence of obesity and psychopathological traits in women with PCOS, the potential association with alterations of the HPA axis, chronic stress and eating behavior or nutrient intake should not be underestimated. This first implies the knowledge of the physiological interaction between the HPA axis and the digestive tract and, second, the interpretation of the neuroendocrine circuits linking the activation of the hypothalamic nuclei regulating the HPA axis and those involved

in the regulation of food intake, the reward system and the response to stress. **(Dallman MF et al., 2004)**

A strong interaction between the HPA axis and the brain - gut axis is well known, although much more information is needed to understand the tuned mechanism involved in this complex network. **(Leal AM et al., 1997)**

For example, both food intake and the light–dark cycle have been found to represent independent synchronizers for the circadian periodicity of cortisol secretion in experimental animals. **(Ishizuka B et al., 1983)**

All the conditions cited earlier may have some relevance in the development of a pathological allostatic load, consistent with a maladaptive response to chronic stress, which explains the association between features of PCOS and metabolic comorbidities, such as abdominal obesity. This may be partly explained by an increased activity of the HPA axis, a key hormonal component of body maladaptation to stress. There are no studies focused on the potential role of chronic stress exposure in the pathophysiology of PCOS and its metabolic comorbidities. One controlled study investigated the neuroendocrine and immune cell response following a public speaking test - which has been proved to induce reproducible and pronounced responses of the HPA axis as well as changes in cytokine levels – showed that both PCOS women and weight-matched controls had comparable increases in state anxiety, blood pressure and C-reactive protein levels, whereas ACTH and cortisol, as well as heart rate responses, were significantly higher in PCOS women, together with a reduced up regulation of IL-6. **(Benson S et al., 2009)**

There are studies focusing on the relationship between psychological distress, hyper androgenemia and menstrual disturbances and their association with greater food cravings and high fat and sweets in hyper androgenic young women, relatively independent of BMI. **(Lim SS et al., 2009)**

3.2.6. GENETICS OF THE HPA AXIS & PCOS

The molecular basis of genetic variation in the HPA axis activity relates to adrenal production of glucocorticoids, their binding to corticosteroid-binding globulin (CBG) and consequently their bioavailability and their efficacy on the transduction mechanisms. Numerous molecular polymorphisms have been described to contribute to physiological as well as to HPA axis-related variations. **(Mormede P et al., 2011)**

Unfortunately, the genetic imprinting of the HPA axis in PCOS has been poorly investigated, in spite of the intensive research of genetic factors involved in the development of androgen excess and metabolic alterations. **(Goodarzi MO et al., 2011)**

The few available studies suggest that genetic factors may play some potential role in the expression of the HPA axis activity in this disorder. One study investigated the sibling correlation of ACTH hormone-stimulated steroid hormone levels between probands with PCOS and their sisters and found that ACTH log-transformed DHEA and cortisol values were significantly correlated between siblings, which supports a potential genetic basis of the adrenal androgen excess observed in PCOS. **(Goodarzi Moet al., 2007)**

Another study found that, in a large cohort of women with hirsutism, including 45% women with PCOS, approximately 20% of women with idiopathic hirsutism and PCOS had increased 17-hydroxyprogesterone and cortisol response to ACTH (1–24) stimulation, supporting the concept that CYP21-carrier status could not explain the observed high prevalence of abnormal ACTH-stimulated adrenal hormone levels. **(Glintborg D et al., 2005)**

A third study assessed the influence of known functional polymorphisms in genes involved in the production, metabolism and signal transduction of steroid hormones in a large cohort of women with or without PCOS**. (Valkenburg O et al., 2011)** This study found that the genotype-frequencies were similar in PCOS cases and population-based controls, although a possible association between glucocorticoid receptor genotype and LH levels was suggested. In fact, the data showed lower LH levels in association with glucocorticoid receptor alleles that are known to increase receptor sensitivity (rs6195 and rs41423247) and higher LH levels in glucocorticoid receptor variants that may inhibit receptor sensitivity (rs6190 and rs6198), supporting the concept that these variants may influence gonadotrophin levels in women with anovulatory PCOS, through modulation of the function of the hypothalomo–pituitary–gonadal axis.

Finally, there are no studies on the genetics of CBG in PCOS, although stress-induced falls in CBG levels may heighten HPA axis responses and CBG: tissue interactions may allow targeted cortisol delivery. There are only preliminary data of altered CBG levels in hypertension and in the metabolic syndrome, but the nature of these associations is uncertain. **(Gagliardi L et al., 2010)**

The genetics of enzymes involved in the metabolism of cortisol in peripheral tissues is discussed in the specific following paragraphs such as infertility, acne, and hirsutism, and possibly negative affect as well.

Cortisol is secreted in response to stressful stimuli in all individuals, and contributes to increased visceral fat **(Drapeau.V et al., 2003)** and increased inflammation. **(Fried.S.K et al., 1998)**

This mechanism could be especially problematic in woman with PCOS since they have more visceral fat and higher inflammatory markers than normal women, and cortisol secretion contributes to hyperandrogenism. Further, a very provocative study reported that lean women with a high waist-to-hip ratio (WHR) secrete more cortisol following both novel *and* familiar cognitive laboratory stressors than do lean women with a low WHR. **(Epel.E.S et al., 2000)**

These results provide evidence that women with a high WHR, unlike those with a lower WHR, tend not to adapt even to familiar stressors, suggesting that they are much more likely to experience elevated cortisol - and, consequently, increased visceral fat - in response to commonly faced stressors. These researchers speculate that maladaptive psychological characteristics such as pessimism, negative affect, passive coping, and greater threat perception may play a role in the bidirectional relationship between cortisol and visceral fat among women with higher WHR.

The above studies not only illustrate cortisol secretion abnormalities among women with PCOS, but also underscore the importance of reducing stress and other maladaptive psychological characteristics in the PCOS woman so as to reduce, as

much as possible, an elevated cortisol response and subsequent visceral fat and hyperandrogenism. Since treatment with metformin may not affect stress reactivity, stress reduction interventions may be important adjunctive approaches when treating women with PCOS.

Another hormone generally elevated among women with PCOS, testosterone, may contribute to increased sympathetic nervous system (SNS) activity.A very interesting study found that exogenous testosterone administration among healthy young women induced cardiac acceleration in response to images of angry faces **(Van Honk.J et al., 2008)**

Since the majority of women with PCOS have elevated testosterone, it is likely that women with PCOS will have an exaggerated sympathetic nervous system response to anger and other negative affect, which may exacerbate inflammation. **(Black.P.H et al., 2003)**

These findings underscore the importance of stress management interventions among PCOS women so as to reduce the adverse physiological changes which can result from psychological stress.

Persistent negative affect and exaggerated SNS activity, then, may exist in the PCOS woman partly due to elevated testosterone alone. The relationship between testosterone and mood, however, is not entirely clear, as one study demonstrated that there is a curvilinear relationship between testosterone levels and depression in women with and without PCOS such that the most severe depression was associated

with levels below and above the normal female range of testosterone. **(Weiner.C.L et al., 2004)**

Negative affect and SNS activation may adversely affect these women by contributing to cortisol abnormalities and chronically elevated inflammation. Normally, inflammation is down-regulated by cortisol, but states of prolonged inflammation (likely to exist in PCOS) result in a phenomenon known as glucocorticoid resistance. In this state, glucocorticoids are no longer able to suppress the production of pro-inflammatory markers **(Raison.C.L. and Miller A.H 2003)**

Depression and sleep disorders are quite common among women with PCOS; and women with PCOS have seemingly-inherent chronic inflammation (thereby rendering them susceptible to glucocorticoid resistance).

Women with PCOS display enhanced sympathetic nervous system and HPA axis activity in response to stressors, which may contribute to increased visceral fat and subsequent inflammation. Interrelations among these abnormalities may create a negative spiral leading to greater insulin resistance and subsequent hyperandrogenism, exacerbating clinical symptoms such as infertility, acne, and hirsutism, and possibly negative affect as well.

3.2.7. STRESS AND MOOD MANAGEMENT

Women with PCOS are likely to exhibit exaggerated SNS responses and HPA-axis abnormalities to negative stimuli, suggesting that teaching them techniques to better manage stressors may offer benefits. In addition to improving mood and decreasing

stress, cognitive behavioral approaches, including stress management interventions, appear in other populations to be capable of normalizing HPA axis regulation. **(Antoni.M.H et al., 2000, Cruess.D.G et al., 2000, Phillips.K.M et al., 2008)** as well as lowering SNS activity. **(Antoni.M.H et al., 2000)**

As such, techniques such as relaxation and cognitive behavioral therapy directed at better managing stress may be used to address the cortisol secretion abnormalities often present in PCOS women, especially since standard treatment with metformin does not appear to affect physiological responses to stress. **(Benson.S et al., 2009)**

Stress management approaches may also have the secondary effects of reducing hyperandrogenism, as has been demonstrated in women with other conditions. **(Cruess.D.G. et al., 2001)**

3.2.8. APPETITE REGULATION

In addition to insulin, other hormones related to obesity are cholecystokinin, the "satiety hormone," and cortisol. Interestingly, secretion of cholecystokinin is reduced among women with PCOS, which causes abnormal appetite regulation, possibly leading to overeating and subsequent obesity. **(Hirschberg.A et al., 2004)**

Likely partially due to obesity but also seemingly inherent in women with PCOS are cortisol level abnormalities; specifically, an increase of peripheral cortisol metabolism due to abnormal levels of certain enzymes that metabolize cortisol (i.e., 5-alpha reductase, 11 beta-hydroxysteroid dehydrogenase). **(Barber.T.M et al., 2006, Rodin.A et al., 1994)**

This increase in cortisol metabolism may result in a decreased negative feedback signal to the HPA axis, thereby maintaining high production of ACTH and, consequently, increased production of adrenal androgens, which exacerbates PCOS symptoms. **(Tsilchorozidou.T et al., 2004)**

Evidence of HPA axis abnormalities among women with PCOS have been demonstrated in several studies and these abnormalities cannot necessarily be attributed to body fat distribution, obesity, or androgen or insulin levels. **(Lanzone.A et al., 1995, Carmina.E et al., 1990)**

3.3 INSULIN RESISTANCE AND PCOS

Insulin resistance appears to contribute to hyperandrogenism and other gonadotropin abnormalities via at least two mechanisms.

First, high concentrations of insulin reduce circulating SHBG levels, resulting in increased bioavailable (free) testosterone, as less SHBG is available to bind with testosterone. **(Nestler, J.E. et al., 1991)**

Second, high insulin concentrations also stimulate androgen biosynthesis from ovaries. **(Nestler J.E. et al., 1998)**

Insulin resistance,frequently appearing in PCOS as well, results in a compensatory hyperinsulinemia, which augments luteinizing hormone (LH) stimulated androgen production, either via its own receptors or via insulin growth factor (IGF-1) receptors.Oxidative stress level is also observed to be significantly correlated with

obesity, insulin resistance, hyperandrogenemia, and chronic inflammation. **(Nasiri.N et al., 2015, González.F. et al., 2012, Federico.A 2007)**

Insulin resistance is believed to play an intrinsic role in the pathogenesis of PCOS. The mechanism by which insulin resistance or insulin give rise to oligomenorrhea and hyperandrogenemia, however, is unclear. Hyperinsulinemiceuglycemic clamp studies have shown that both obese and lean women with PCOS have some degree of insulin resistance.Insulin resistance is implicated in the ovulatory dysfunction of PCOS by disrupting the hypothalamic pituitary ovarian axis.Given the association with insulin resistance, all women with PCOS require evaluation for the risk of metabolic syndrome (MetS) and its components, including type 2 diabetes, hypertension, hyperlipidemia, and the possible risk of clinical events, including acute myocardial infarction and stroke. Obese women with PCOS are at increased risk for MetS with impaired glucose tolerance (IGT; 31 to 35%) and type 2 diabetes mellitus (T2DM; 7.5 to 10%). Rates of progression from normal glucose tolerance to IGT, and in turn to T2DM, may be as high as 5 to 15% within 3 years. **(Goodman.N.F et al., 2015)**

Numerous studies have documented that insulin resistance is common in both obese and lean women with PCOS. **(Sharma.S.T. and Nestler.J.E, 2006)**

In fact, 70% of women with PCOS are insulin resistant **(González. F et al., 2006)**

The hyperinsulinemic state present in most women with PCOS appears to play a central role in PCOS development and is considered to be the cause rather than the result of hyperandrogenism **(Tsilchorozidou.T et al., 2004)**

Studies supporting this hypothesis reveal that antiandrogen therapy does not improve insulin resistance. **(Diamanti-Kandarakis et al., 1995)** while insulin-sensitizing agents (i.e., metformin) not only improve insulin sensitivity but also improve menstrual abnormalities and reproductive outcomes in women with PCOS, providing indirect evidence of reduced hyperandrogenism. **(Moghetti.P et al., 2000)**

As many as 70% of PCOS women are insulin resistant and 10% have DM. (**Farrell.K and Antoni.M.H 2010, Ovalle.F and Azziz.R 2002)** In PCOS women with normal glucose metabolism initially, the rate of conversion to abnormal glucose metabolism can be 25% over just three years**. (Pesant.M.H and Baillargeon.J.P 2011)**

More alarming, insulin abnormalities are highly prevalent in adolescents with PCOS. (**Bhattacharya.S.M. and Ghosh.M 2010**) The routine use of OGTT is advocated by some in all PCOS women. **(Katz.A et. al., 2000)**

In teenagers, abnormalities in glucose metabolism manifest prior to dyslipidemia, suggesting that assessment of glucose metabolism is even more important in younger women. **(Fulghesu.A et al., 2010)**

Approximately 50% to 70% of all women with polycystic ovary syndrome (PCOS) have some degree of insulin resistance, and this hormone insensitivity probably contributes to the hyperandrogenism that is responsible for the signs and symptoms of PCOS.The OGTT is probably the best simple, officebased method to assess women with PCOS because it provides information about both insulin resistance and glucose intolerance. The diagnosis of glucose intolerance holds greater prognostic and treatment implications. **(Legro.R.S et al., 2004)**

A substantial proportion of PCOS patients have abnormalities on the oral glucose tolerance testing at the time of diagnosis. When assessed overall (obese and lean together) PCOS patients had a 31% rate of impaired glucose tolerance and 7.5% met the criteria for type 2 diabetes mellitus. **(Legro R et.al., 2004)**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. **(Legro RS et al., 1999)**

In those with normal glucose tolerance at baseline 17% had developed impaired glucose tolerance or type 2 diabetes mellitus over time, while 54% of those with impaired glucose tolerance at baseline had progressed to type 2 diabetes mellitus. Further support for the high prevalence of abnormal glucose tolerance in PCOS is the 10-fold increased risk of developing gestational diabetes mellitus compared to the general population (baseline risk ~3%). **(Glueck CJ et al., 2001)**

Metformin therapy throughout pregnancy reduces the development of gestational diabetes in women with polycystic ovary syndrome. **(Glueck CJ et al., 2002)**

Lastly, Cibula et al. noted a 4-fold increased prevalence of type 2 diabetes mellitus in women with PCOS who had undergone ovarian wedge resection for polycystic ovaries some 20 to 40 years earlier compared to a closely matched control population **(Cibula D 2000)**

3.4 HYPERANDROGENEMIA

Hyperandrogenemia is a classical feature of polycystic ovary syndrome (PCOS), and 70%–80% of women with hyperandrogenemia are diagnosed with PCOS. **(Nisenblat.V and Norman.R.J 2009)**

Hyperandrogenemia is regarded as the core pathogenesis of PCOS, as PCOS models of animals could be established by excess androgen administration **(Nisenblat.V and Norman. R.J 2009, Masszi.G et al., 2013)** For the increased androgen levels in PCOS, insulin resistance (IR) is regarded as the primary factor, by compensatory hyperinsulinemia. **(Bremer.A.A and Miller.W.L 2008)**

Insulin is reported to stimulate ovarian androgen secretion directly alone and/or augment luteinizing hormone-(LH-) stimulated androgensecretion. **(Barbieri.R.L et al., 1986, Yelich.J.V et al., 1996, Hernandez.E.R et al., 1988)**

In addition, insulin may also enhance the amplitude of gonadotropin-releasing hormone- (GnRH-) stimulated LH pulses, decrease hepatic production of serum sex hormonebinding globulin (SHBG), and/or decrease insulin-like growth factor binding protein-1 (IGFBP-1). **(Adashi.E.Y et al., 1981, R.Soldani.A.et al., 1994, Nestler.J.E et al., 1991)**

Finally, the availability of free insulin-like growth factor-1 (IGF-1) is increased to stimulate androgen production. **(Ibáñez.L et al., 1997, Werner.H et al., 1993)**

3.4.1. CLINICAL HYPERANDROGENEMIA

Hirsutism—Hirsutism in females is defined as the presence of terminal hairs on the face and/or body in a male-type pattern, and it affects 65–75% of the population with PCOS. **(Azziz.R et al., 2006)**

Hirsutism is determined by using a visual score system, Ferriman and Gallwey **(Ferriman.D and Gallwey.J.D 1961, Yildiz.B.O et al., 2009)** that evaluates nine body areas, including: the upper lip; chin; chest; upper back; lower back;upper and lower abdomen; upper arm and thigh. The areas are assigned a score of 0–4 based on the density of terminal hairs. A score of 0 represented the absence of terminal hairs, a score of 1 minimally evident terminal hair growth, and a score of 4 extensive terminal hair growths.

3.5. CHRONIC LOW-GRADE INFLMMATION AND OXIDATIVE STRESS IN RELATION TO INSULIN RESISTANCE

Inflammation and oxidative stress have been related to the pathogenesis of PCOS. **(Zhao.Y et al., 2015, Escobar-Morreale.H.F et al., 2011)**

Oxidative stress, inflammation could induce insulin resistance (IR) mainly via interfering with post-insulin receptor signaling pathway, insulin receptor substrate 1-phosphatidyl inositol 3 kinaseprotein kinase B (IRS1-PI3K-PKB/Akt) pathway. **(Keane.K.N et al., 2015)**

Chronic low-grade inflammation is considered as an important feature of polycystic ovary syndrome (PCOS) and has been suggested to participate in the pathogenesis and

development of PCOS.Inflammation has also been demonstrated to be associated with IR in PCOS. **(González.F et al., 2006)**

It was reported that adipose derived TNF-α levels in mice were increased during the advancement of obesity, but when TNF-α was neutralised, insulin sensitivity was improved **(Hotamisligil.G.S et al., 1993)**

Oxidative stress (OS) and inflammation seem to contribute to hyperandrogenemia in PCOS, but detailed interactions still remain unclear, as few investigations have been discovered to focus on the subject. In multiinvestigations, OS and inflammation markers are discovered to be positively correlated with androgen levels in PCOS patients **(Yang.Y et al., 2011)**

Oxidative stress has been implicated in the etiology of IR in leukocytes from PCOS patients, and an increase in leukocytes has been highlighted as a putative marker of low-grade chronic inflammation and early cardiovascular risk in these subjects. **(Escobar-Morreale.H.F et al., 2011)**

One study found that C - reactive protein (CRP), an inflammatory marker that has been shown to predict cardiovascular events in previously healthy women. **(Sesso, H.D et al., 2003)** was significantly higher in women with PCOS and PCO than in controls and this difference could not be attributed to age, BMI, waist-to-hip ratio, and lipid profile. **(Engin-Üstün et al., 2006)**

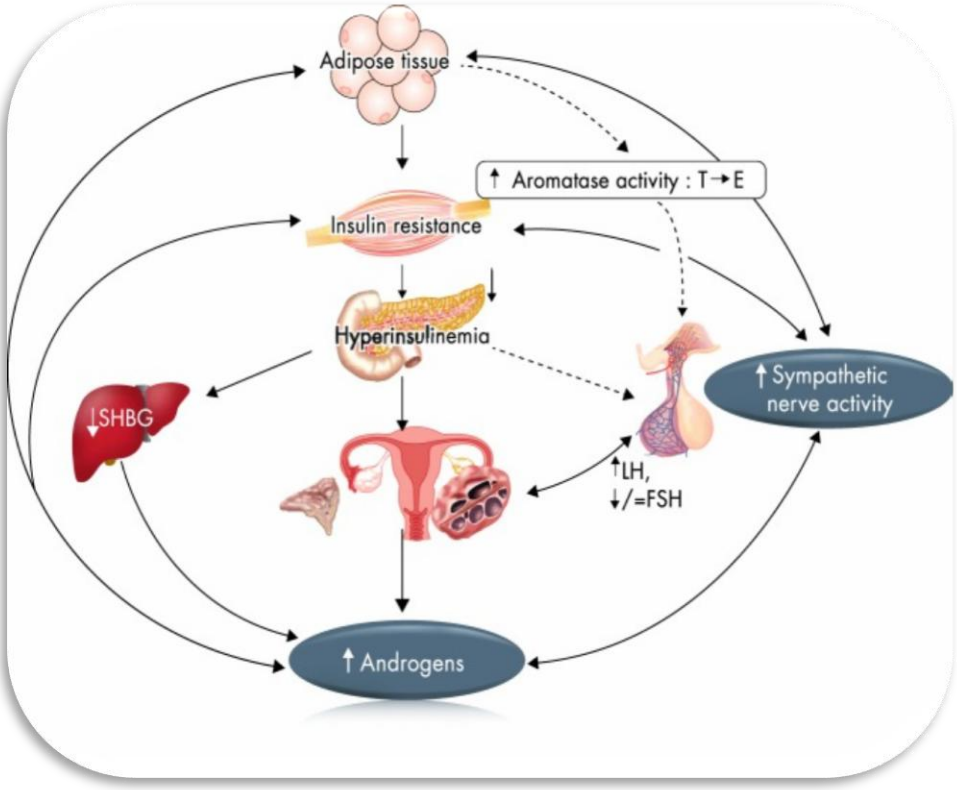
3.6. INTERACTIONS BETWEEN GENETIC, METABOLIC, FETAL, AND ENVIRONMENTAL FACTORS.

PCOS is complex and reflects the interactions between genetic, metabolic, fetal, and environmental factors. Among these factors, disordered gonadotropin secretion, hyperandrogenemia, insulin resistance and perinsulinemia, ovarian dysfunction, and follicular arrest are prominent. Several theories have been proposed to explain the pathogenesis of PCOS. One of these is that neuroendocrine defects lead to increased pulse frequency and amplitude of LH and relatively low FSH. This causes…..

Several theories have been proposed to explain the pathogenesis of PCOS. One of these is that neuroendocrine defects lead to increased pulse frequency and amplitude of LH and relatively low FSH.

In normal women, the adrenal glands and the ovaries secrete androgens in response to ACTH and LH, respectively. **(Rosenfield R.L., 1999)** Approximately half of the androgen production stems from direct secretion and half from enzymes peripherally converting 17ketosteroids into androstenedione (predominantly) in skin, liver, and adipose tissue. **(Bachmann.G et al., 2002)**

The hypothalamicpituitary axis does not directly regulate androgen production in the adrenal glands, and intraglandular autocrine and paracrine factors also influence androgen production throughout the body. **(Ehrman.D.A et al., 1995)**



A consistent feature of PCOS is disordered gonadotropin secretion with elevated mean LH, low or low normal FSH and a persistently rapid frequency of GnRH pulse secretion. **(Zumoff. B et al., 1983, Kazer.R.R et al., 1987)**

3.6.1. ABNORMAL PITUITARY FUNCTION

Under normal circumstances, the hypothalamic gonadotropin-releasing hormone (GnRH) pulses cause luteneizing hormone (LH) and follicle-stimulating hormone (FSH) release. LH stimulates ovarian theca cells to produce androgens (mainly androstenedione) and FSH stimulates granulosa cells to convert the androstenedione to estrone and estradiol. **(McNatty K.P et al., 1979)**

Estrogen and progesterone provide negative feedback to GnRH-secreting neurons as well as the pituitary. Adolescents with PCOS have increased LH levels above average

follicular phase levels as well as increased pulse secretion. **(Blank.S.K et al 2006, Taylor.A.E et al., 1997)** This pattern is exaggerated in adolescents with increased adiposity. **(Kasa-Vubu et al., 2010)**

Higher LH levels increase thecal production of androgens, which in turn will counteract the LH-suppressive role of female hormones as well as regulation of GnRH neurons by progesterone. **(Berga.S.L et al., 1993, Eagleson.C.A et al., 2000, Turgeon.J.L and Waring D.W 1999)**

Insulin resistance and the consequent development of hyperinsulinemia appear to be central in the pathophysiologic mechanism that links PCOS to its concurrent metabolic derangements. Compensatory hyperinsulinemia is important in the development of metabolic abnormalities and also contribute to the high androgen levels observed in women with PCOS. Insulin binds to its cognate receptor on the ovarian theca cell, enhancing the luteinizing hormone (LH)-stimulated androgen production. **(Barbieri.R.L et al., 1986, Nestler.J.E et al., 1991, Nestler.J.E et al., 1998, Codner.E et al., 2007, Diamanti-Kandarakis.E et al 2008)**

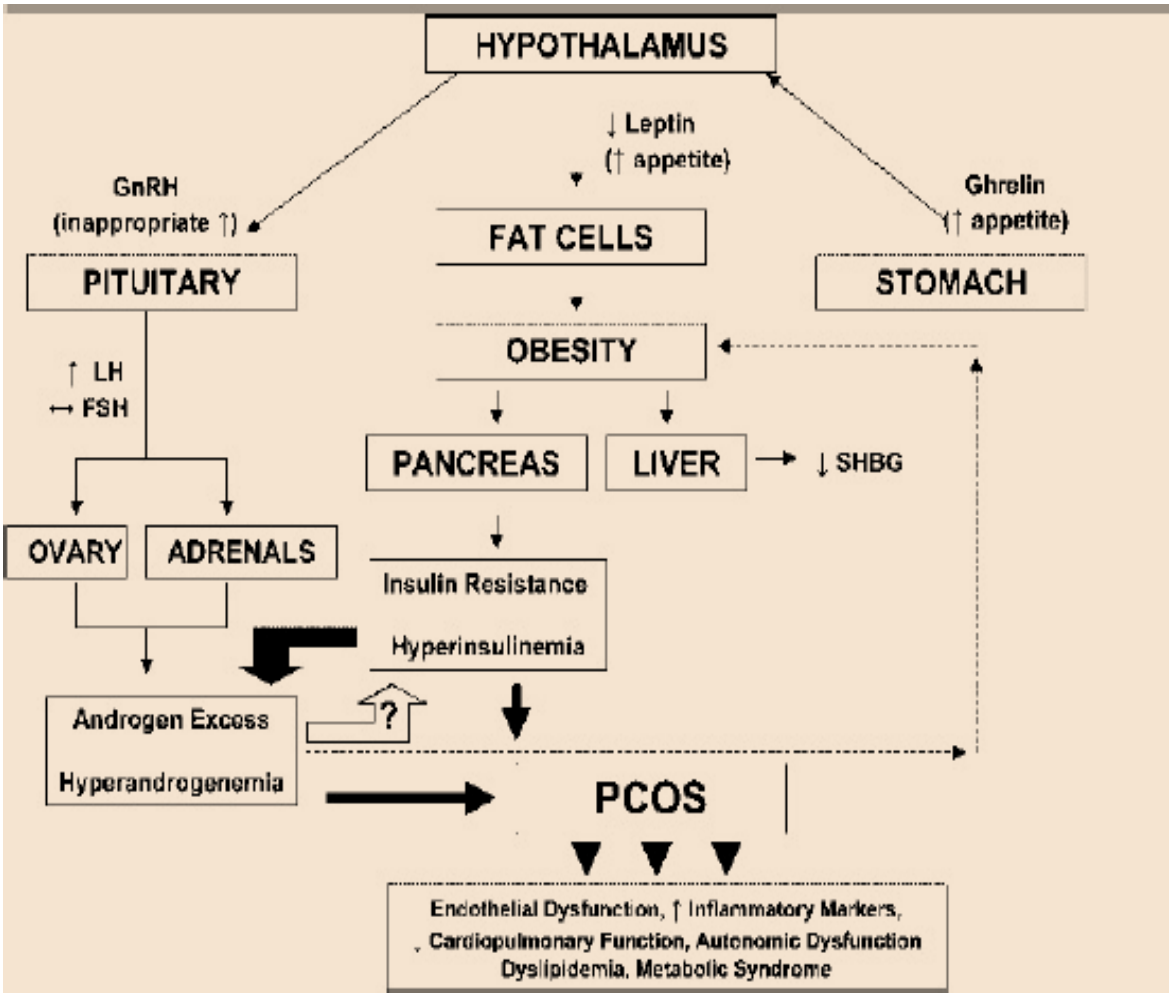
Clinical evidence suggests that elevated insulin levels cause hyperandrogenism, and not the other way around, as show n by the decrease in serum androgen levels observed when circulating insulin concentrations are lowered by the administration of insulin-sensitizing drugs or drugs that inhibit insulin secretion.

Insulin can also act indirectly to raise the serum concentration of free testosterone, the level of which does not seem to be tightly regulated in women, by inhibiting the hepatic production of sex-hormone–binding globulin (SHBG).

Clinical studies have shown that hyperandrogenism is linked with insulin resistance/metabolic syndrome in PCOS women. There are several potential mechanisms for the association of androgen excess with insulin resistance, including both direct and indirect actions of androgens on insulin target tissues. Studies to define the molecular mechanisms whereby androgens interact with insulin effects on glucose metabolism in target tissues, as well as the regulation of local androgen production in the adipose tissue and its role in metabolism, are required. Exercise training and diet efficiently decrease fasting insulin levels and also improve hyperandrogenism by increasing SHBG and decreasing androgen levels. Whether in conjunction with pharmacotherapy or as a stand-alone treatment, lifestyle modifications (diet and exercise training) certainly represent a fundamental strategy for the treatment of women with PCOS.

Figure 1 Flowchart illustrating the relationship between insulin resistance and androgens in PCOS. Clinical evidence suggests that elevated insulin levels cause hyperandrogenism, and not the other way around, as shown by the decrease in

serum androgen levels observed when circulating insulin concentrations are lowered by the administration of insulin-sensitizing drugs or drugs that inhibit insulin secretion



https://www.researchgate.net/publication/26295382_Androgens_in_Polycystic_Ovay_Syndrome_The_Role_of_Exercise_and_Diet.

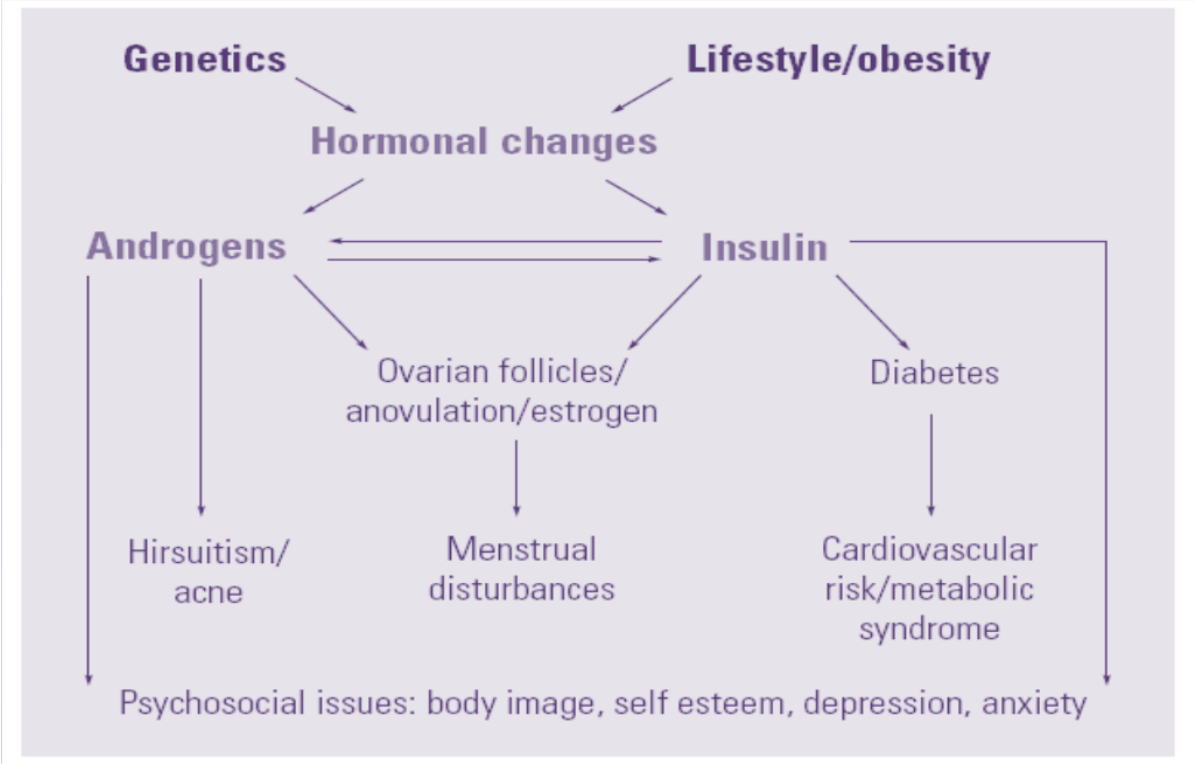
The association between insulin resistance, compensatory hyperinsulinemia and hyperandrogenism has provided insight into the pathogenesis of the PCOS. The insulin resistance may occur irrespective of BMI, the common association of PCOS and obesity has a synergistic deleterious impact on glucose homeostasis and can worsen both hyperandrogenism and anovulation. Insulin acts through multiple sites to increase endogenous androgen levels. Increased peripheral insulin resistance results in a higher serum insulin concentration.

Excess insulin binds to the IGF-1 receptors that enhance the theca cells' androgen production in response to LH stimulation. Hyperinsulinemia also decreases the synthesis of SHBG by the liver. Therefore, there is an increase in serum free testosterone concentration and consequent peripheral androgen action.

The clinical outcome measures of the study were the improvement in the regularity of the menstrual cycle, the BMI and the improvement in the modified Ferriman - Gallwey (F-G) score for hirsutism. The biochemical outcome measures will be the change in the Serum free testosterone, dehydroepiandrosterone (DHEA), fasting insulin level, Glcosylated hemoglobin (HbA1c) and Low Density Lipoproteins (LDL) levels.

Hyperandrogenism is a well established contributor to PCOS aetiology, detected in around 60% to 80% of cases. Insulin resistance is a pathophysiological contributor in around 50% to 80% of women with PCOS, especially in those with more severe PCOS diagnosed on National Institutes of Health (NIH) criteria and in women who are overweight. **(Legro RS et al., 2004).**

Genetic and environmental contributors to hormonal disturbances combine with other factors, including obesity, ovarian dysfunction and hypothalamic pituitary abnormalities to contribute to the aetiology of PCOS. Picture .1 (**Legro RS et al., 2002, Doi SA et al., 2005)**



Picture.1 GENETIC AND ENVIRONMENTAL CONTRIBUTORS

3.7. OBESITY RELATION WITH INSULIN RESISTANCE

Considering the baseline defects in insulin sensitivity and secretion in PCOS and the deleterious impact of obesity on these measures, women with this condition are expected to have a high prevalence of impaired glucose tolerance (IGT, defined by a 2h post-challenge glucose level 140–200 mg/dl) and Type 2 diabetes. The risk for developing glucose intolerance increased with increasing body mass index (BMI); the prevalence of IGT and type 2 diabetes were much lower in nonobese women with PCOS (10.3% and 1.5%, respectively) compared to the obese and the overall population.

Obese women are more likely to have menstrual irregularity and anvolatory infertility than normal-weight women. In reproductive-age women, the relative risk of

anovulatory infertility increases at a BMI of 24 kg/m2 and continues to rise with increasing BMI. **(Rich-Edwards JW et al., 2002)**

The insulin resistance may occur irrespective of BMI, the common association of PCOS and obesity has a synergistic deleterious impact on glucose homeostasis and can worsen both hyperandrogenism and anovulation. Insulin acts through multiple sites to increase endogenous androgen levels. Increased peripheral insulin resistance results in a higher serum insulin concentration. Excess insulin binds to the IGF-1 receptors that enhance the theca cells' androgen production in response to LH stimulation. Hyperinsulinemia also decreases the synthesis of SHBG by the liver. Therefore, there is an increase in serum free testosterone concentration and consequent peripheral androgen action.

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About 42% of patients with polycystic ovary syndrome (PCOS) have the complication of obesity. **(March, W.A et al., 2009)**

Abdominal obesity is regarded as a common complication of PCOS, and the risk of abdominal obesity in PCOS women ranges from 40% to 80% because of the differences of people and nations. **(Gambineri.A et al., 2001)**

Body mass index (BMI) is used as a popular criterion in clinic to evaluate obesity; however, about 50% of PCOS patients with normal BMI still have abdominal obesity. **(Kirchengast.S and Huber.J 2001)**

Another study found that IL-18 was higher in lean and obese PCOS participants compared to controls matched for BMI and smoking status. **(Escobar-Morreale. H.F et al., 2004)**

Consistent with a pathophysiologic role for obesity, weight reduction can restore regular menstrual cycles in these women PCOS is associated with high rates of glucose intolerance resulting from defects in insulin action and β-cell function. Obesity substantially exacerbates these defects so obese reproductive-age women with PCOS are at very high rates of glucose intolerance. Detection of glucose abnormalities in women with PCOS is best performed by means of glucose tolerance testing, since fasting glucose levels may be normal despite presence of glucose intolerance. In reproductive-age women, the relative risk of anovulatory infertility increases at a BMI of 24 kg/m2 and continues to rise with increasing BMI consistent with a pathophysiologic role for obesity, weight reduction can restore regular menstrual cycles in these women.

In obesity increased androgen production has been reported especially in women with upper-body obesity. This abnormality is further worsened by obesity, especially central obesity, since sex hormone binding globulin, or SHBG, levels are reduced in this state due to hyperinsulinemia. PCOS is characterized by abnormalities in the gonadotropin hormone releasing hormone, or GnRH, pulse generator leading to

preferential increase in LH release over follicle stimulating hormone (FSH).Independent of BMI, women with PCOS have been reported to have a high prevalence of upper-body obesity as demonstrated by increased waist circumference and waist-hip ratio compared to BMI-matched control women.

The Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society recommends an assessment of CVD risk factors in women with PCOS and assignment of PCOS related CVD risk categories. The "at risk category women with PCOS who also display includes obesity (especially abdominal adiposity), cigarette smoking, hypertension, dyslipidemia (increased LDL-C and/or non-HDL-C), subclinical vascular disease, IGT and a family history of premature CVD (<55 yr of age in male relative, < 65 yr of age in female relative). Women with PCOS who also meet criteria for the metabolic syndrome, type 2 diabetes mellitus and overt vascular or renal disease are considered to be high risk for CVD. **(Wild, Carmina, 2010)**

This group recommended that BP, waist circumference and BMI be determined at every visit, a lipid profile (total cholesterol, LDL-C, non-HDL-C, HDL-C, and triglycerides) be obtained every 2 years and a 2-h post 75-g oral glucose challenge be performed with a BMI greater than 30 kg/m2, or alternatively in lean PCOS women with advanced age (>40 yr), personal history of gestational diabetes, or family history of T2DM. Screening for depression, anxiety and quality of life was also suggested. **(Dokras, 2011)** The recent 3rd PCOS Consensus Workshop Group recommended CVD risk assessment at any age is for psychosocial stress, blood pressure, glucose, lipid profile (cholesterol, triglycerides, HDL, LDL, and non-HDL cholesterol), waist circumference, physical activity, nutrition, and smoking. **(Fauser, 2012)**

The cause of insulin resistance is likewise complex and multifactorial with genetic and environmental contributors. Women with PCOS are at increased risk of developing IGT and DM2 with prevalence rates of 31.3% and 7.5%, respectively, compared to 14% for IGT and 0% for DM2 in age-matched and weight-matched non-PCOS control women. It is increasingly clear that IGT is also a clinically relevant state where early dentification and intervention improve long-term outcomes. IGT has been found to increase the risk of CVD, mortality and progression to DM2 in general populations. Recent population based data noted a mortality rate of 5.5% over 5 years for those with IGT versus 1.9% with normal glucose tolerance. Furthermore, lifestyle intervention, metformin and glitazones can prevent IGT progression to DM2, strengthening the argument for early detection of IGT, including in high-risk PCOS women. There are currently no generic guidelines for IGT screening, only for DM2 based on fasting glucose or more recently on HbA1c as a first line.

MANAGEMENT OF OBESITY IN PCOS

Weight loss reduces hyperinsulinemia and subsequently hyperandrogenism. In the study by Kiddy et al. discussed earlier, about 40% of obese women with PCOS (mean body mass index [BMI] ~34 kg/m2) who lost >5% of initial body weight with caloric restriction achieved spontaneous pregnancy. **(Kiddy DS et al., 1992)**

3.8. GLUCOSE METABOLISM

Consistent with a pathophysiologic role for obesity, weight reduction can restore regular menstrual cycles in these women. PCOS is associated with high rates of

glucose intolerance resulting from defects in insulin action and β-cell function.Obesity substantially exacerbates these defects so obese reproductive-age women with PCOS are at very high rates of glucose intolerance. Detection of glucose abnormalities in women with PCOS is best performed by means of glucose tolerance testing, since fasting glucose levels may be normal despite presence of glucose intolerance.In reproductive-age women, the relative risk of anovulatory infertility increases at a BMI of 24 kg/m2 and continues to rise with increasing BMI. Consistent with a pathophysiologic role for obesity, weight reduction can restore regular menstrual cycles in these women.

In obesity increased androgen production has been reported especially in women with upper-body obesity. This abnormality is further worsened by obesity, especially central obesity, since sex hormone binding globulin, or SHBG, levels are reduced in this state due to hyperinsulinemia. PCOS is characterized by abnormalities in the gonadotropin hormone releasing hormone, or GnRH, pulse generator leading to preferential increase in LH release over follicle stimulating hormone (FSH).Independent of BMI, women with PCOS have been reported to have a high prevalence of upper-body obesity as demonstrated by increased waist circumference and waist-hip ratio compared to BMI-matched control women.

A substantial proportion of PCOS patients have abnormalities on the oral glucose tolerance testing at the time of diagnosis. When assessed overall (obese and lean together), PCOS patients had a 31% rate of impaired glucose tolerance and 7.5% met the criteria for type 2 diabetes mellitus.**(Legro RS et al., 1999)**

In those with normal glucose tolerance at baseline 17% had developed impaired glucose tolerance or type 2 diabetes mellitus over time, while 54% of those with impaired glucose tolerance at baseline had progressed to type 2 diabetes mellitus. Further support for the high prevalence of abnormal glucose tolerance in PCOS is the 10-fold increased risk of developing gestational diabetes mellitus compared to the general population (baseline risk ~3%). **(Glueck CJ et al., 2002)**

Lastly, Cibula et al. noted a 4-fold increased prevalence of type 2 diabetes mellitus in women with PCOS who had undergone ovarian wedge resection for polycystic ovaries some 20 to 40 years earlier compared to a closely matched control population. **(Cibula D et al., 2000)**

PCOS was associated with an increase in glucose abnormalities, suggesting that obese PCOS adolescent are at increased risk for developing glucose intolerance (IGT) and T2DM compared with their non-PCOS counterparts. **(Harwood K et al., 2007, Rossi.B et al., 2008)**

The prevalence of IGT (fasting blood glucose levels of 100–125 mg/dl, and/or 2 h postprandial glucose level after a 75 g oral glucose challenge between 140–200 mg/dl) is not clear. Bridger *et al*., showed that in a study of 22 obese adolescents with PCOS, only one participant had IGT (4.5%). **(Bridger.T et al., 2006)**

Others studies involving obese adolescents with PCOS report rates of IGT as high as **(Palmert M.R et al., 2002)** to 52%. **(Arslanian S.A et al., 2001)**

By contrast, nonobese adolescents with evidence of PCOS or ovarian hyperandrogenism do not seem to have an increased risk of IGT as shown in studies carried out. **(Ibanez et al., 2000, Silfen M.E et al., 2003)**

As adults, the most reliable screening test for IGT in PCOS adolescents is the 2-hr OGTT after a 75-g glucose load interpreted using ADA guidelines. **(Salley, K.E et al., 2007)**

This is an interesting paper that reviews ADA guidelines. Although the most appropriate screening interval is not clearly defined, the conversion from IGT to T2DM can occur in as little as 5years most likely because of the strong correlation of PCOS and insulin resistance and β-cell failure. **(Saad.R et al., 2005)**

3.9. CARDIOVASCULAR RISK FACTORS

Cardiovascular Risk Factors and Disease in PCOS studies have shown either a greater prevalence of diagnosed hypertension or higher ambulatory blood pressure in PCOS. The pattern of dyslipidemia in PCOS is in keeping with IR, increased triglycerides, and low HDL-cholesterol. **(Wild RA et al., 1985, Wild RA et al., 1992, Slowinska-Srzednicka J et al., 1991, Talbott E et al., 1995)**

Dyslipidemia The prevalence of at least one abnormal lipid level by National Cholesterol Education Program guidelines approaches 70%. **(Legro, R.S et al., 2001)** in adolescents, PCOS. (**Demirel.F et al., 2007)**

Women with PCOS may also have higher levels of small, dense LDL-cholesterol **(Pirwany.IR et al., 2001),** homocysteine **(Loverro G et al., 2002),** plasminogen

activator inhibitor type 1 **(Velazquez EM et al, 1997),** decreased insulin induced vascular relaxation **(Kelly CJ et al 2002)** and endothelial dysfunction**. (Paradisi G et al., 2000)** 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. **(Wild.RA et al., 1990, Birdsall.MA et al., 1997)**

The Nurses' Health Study cohort revealed that women with "usually irregular" or "very irregular" menstrual cycles had an increased risk of coronary artery disease events of approximately 20% and 60%, respectively versus those with "very regular" cycles. **(Solomon.CG et al., 2002)** Cibula et al. reported a 4-fold increased risk of coronary artery disease in PCOS patients followed 20 to 40 years.

The cause of insulin resistance is likewise complex and multifactorial with genetic and environmental contributors. Women with PCOS are at increased risk of developing IGT and DM2 with prevalence rates of 31.3% and 7.5%, respectively, compared to 14% for IGT and 0% for DM2 in age-matched and weight-matched non-PCOS control women. It is increasingly clear that IGT is also a clinically relevant state where early identification and intervention improve long-term outcomes. IGT has been found to increase the risk of CVD, mortality and progression to DM2 in general populations. Recent population based data noted a mortality rate of 5.5% over 5 years for those with IGT versus 1.9% with normal glucose tolerance. Furthermore, lifestyle intervention, metformin and glitazones can prevent IGT progression to DM2, strengthening the argument for early detection of IGT, including in high-risk PCOS women. There are currently no generic guidelines for IGT

screening, only for DM2 based on fasting glucose or more recently on HbA1c as a first line.

Alongside insulin resistance, metabolic syndrome, IGT and DM2, women with PCOS also have increased novel cardiovascular risk factors (inflammation, oxidative stress and impaired fibrinolysis).Given that large longitudinal cohort studies have reported up to 65% of CVD deaths occur in subjects with impaired glucose metabolism and that IGT and DM2 are increased in PCOS, it would be expected that women with PCOS would have increased CVD risk.

Addressing hyperandrogenism is clinically important and monitoring for and managing longer-term metabolic complications, including dyslipidaemia, IGT, DM2, and cardiovascular risk factors, is crucial. Consideration should be given to screening high-risk family members for metabolic abnormalities also. Overall, further research is needed in this complex condition. In the interim, comprehensive evidence-based guidelines are needed to guide consumers and clinicians in optimal PCOS management.

CARDIO METABOLIC ASPECTS OF POLYCYSTIC OVARIAN SYNDROME

The prevalence of obesity in PCOS varies widely, between approximately 10–50%.Obese PCOS have lower levels of luteinizing hormone (LH), sex hormone bindingglobulin (SHBG), dehydroepiandrosterone (DHEAS), dihydrotestosterone, free insulin-like growth Factor (IGF)-I, high-density lipoprotein, and higher low-density lipoprotein, compared with the nonobese PCOS group.

3.10. BLOOD PRESSURE IN PCOS

Etiology of hypertension that occurs in the setting of PCOS is also multifactorial, including factors such as hyperandrogenemia, insulin resistance, obesity, and increased sympathetic nervous system activity.

Androgen Excess - There are data demonstrating that the hyperandrogenemia in PCOS women is associated with systolic and diastolic blood pressures in women with PCOS, independent of obesity or insulin resistance. **(Chen.M.J et al., 2007)**

Androgen excess has also been associated with an increase in cIMT in women with PCOS. **(Luque-Ramírez.M et al., 2007)** Increased cIMT has been widely used as a reflection of preclinical atherosclerotic disease, a contributor to the development of hypertension.

Hypertension may be secondary to enhanced sodium retention occurring in the setting of hyperinsulinemia. High insulin levels have been associated with a subsequent increase in intracellular sodium and calcium. **(Resnick.L.M. 1992)** Obesity is a well-established risk factor for hypertension and it has been considered the primary etiology implicated in the increased blood pressure in women with PCOS. **(Luque-Ramírez.M et al., 2007)**

Greater sympathetic nerve activity was found in a study of 20 women with PCOS who were compared to 18 weights and age-matched control women. **(Sverrisdottir.Y.B et al., 2008)**

The sympathetic nerve activity to the muscle vascular bed among women with PCOS was increased and highly correlated with testosterone level and to a lesser degree the cholesterol level. In addition, androgen excess as well as insulin resistance **(Muniyappa.R et al., 2007)** and obesity. **(Müller-Wieland.D et al., 1998)** have been implicated in stimulating the autonomic nervous system, thereby, each serving as a potential mediator of the hypertension observed in PCOS.

Hypertension is a significant contributor to the risk for cardiovascular disease. The increased prevalence of hypertension in women with PCOS may contribute to the increased risk of cardiovascular disease in women with PCOS. Thus, the Androgen Excess and Polycystic Ovarian Societies recommend that blood pressure be obtained in women with PCOS at every visit and that prehypertension be detected and treated given the potential benefit of lowering blood pressure for the prevention of CVD. **(Wild.R.A et al., 2010)**

In the Nurses' Health Study, a history of menstrual cycle irregularity was associated with an increased risk of non-fatal and fatal coronary heart disease. **(Solomon et al., 2002)** This might be explained by a high rate of PCOS with its associated metabolic disturbances in these women, although no other clinical or biochemical androgen data was available to confirm that menstrual irregularity was due to PCOS.

3.10. PREVALENCE OF PCOS

Prevalence of polycystic ovary syndrome in young women from North India: A Community based study

The prevalence reported in earlier studies varies between 2.2% to 26%. These variations are due to difficulties in hormonal evaluation and lack of consensus on diagnostic criteria. Insulin resistance is central to the pathogenesis of PCOS, and Indians are known to have high prevalence of insulin resistance, so the prevalence of PCOS may be high in our population. Prevalence of PCOS in young women (18-25 years) was 3.7%, and majority of them were lean. Even at this young age, these women were at a high risk of metabolic syndrome because of the increased prevalence of abnormal waist hip ratio and prehypertension. **(Knochenhauer.E.S et al., 1998, Azziz.Ret al., 2004, Diamanti-Kandarakis.E et al., 1999, March.W.A et al., 2009)**

Metabolic syndrome is another cluster of endocrine disturbances, including insulin resistance, dyslipidemia, obesity, and hypertension. **(Ma.Y.M et al., 2010)**

It is associated with a two-fold increased risk of cardiovascular disease and a five-fold increased risk of type 2 diabetes. **(Kumarapeli.V et al., 2008)**This illustrates the importance of early detection of insulin resistance and metabolic syndrome with subsequent application of preventive measures in women with polycystic ovary syndrome.

3.11. PHARMACOLOGICAL INTERVENTIONS -

INSULIN SENSITIZERS

Metformin is effective in the treatment of metabolic syndrome and modestly increases menstrual regularity and ovulation, and may improve hirsutism in patients with PCOS. **(Harborne et al., 2003)**

Metformin treatment in lean women with PCOS also improves insulin resistance and hyperandrogenism without a change in BMI. **(Nestler and Jakubowicz 1997)** Whilst metformin appears to induce cardio-protective effects on serum insulin **(Sahin et al 2004)**, serum lipids **(Ibanez et al 2004)**, and PAI-1 **(Song et al 2002)**, the actual protection from long-term mortality and morbidity of cardiovascular disease has yet to be demonstrated. In addition, it has been suggested that metformin has a beneficial effect on endothelial function in patients with polycystic ovarian syndrome. **(Orio et al., 2005)**

3.12 YOGANIDRA INTERVENTIONS FOR PCOS

The characteristic feature of YogaNidra was the systematic rotation of consciousness in the body, which originated from the tantric practice of Nyasa (meaning to place or to take the mind to that point).Nyasa, was practiced in a sitting posture and involved the use of specific mantras which were placed, felt or experienced at different parts of the body. First the name of the part was recited, then it was visualized or touched, and the mantra was placed there. Nyasa was a means of concentrating the physical

body by instilling higher awareness or divine consciousness into the various parts during tantric ritual practice.

In YogaNidra perhaps the most effective means of training the mind is found in Sankalpa, which you make for yourself during each practice. Anything in life can fail you, but not the Sankalpa made during YogaNidra. Sankalpa is an important stage of YogaNidra and a powerful method of reshaping your personality and direction in life along positive lines.

The Sankalpa takes the form of a short mental statement which is impressed on the subconscious mind when it is receptive and sensitive to autosuggestion during YogaNidra.

During anxiety, there is an increased response of hypothalamus and heightened sympathetic activity. YogaNidra appears to regulate hypothalamus, in a way resulting in decreased sympathetic (excitatory) nervous activity and increased parasympathetic (inhibitory) function. **(Satyananda S. YogaNidra 2009)**

Khushbu Rani et al., 2016 found significant decrease in their degree of depressive symptoms (according to the psycho-biological general wellbeing Index).There was significant change in TSH, FSH, LH, and Prolactin levels in intervention group as compared to the control group.

Previous studies found that long term practice of yoga lead to decreased TSH, growth hormone, and prolactin imbalances significantly. Metabolic effects of meditation (YogaNidra) includes a decreased adrenocortical activity, long term decreased

cortisol secretion and lesser thyroid stimulating hormone (TSH) abnormalities. **(Schell FJ et al., 1994)**

Metabolic effects of meditation (YogaNidra) includes a decreased adrenocortical activity, long term decreased cortisol secretion and decreased thyroid stimulating hormone (TSH). Imbalances in the hormonal profile also predispose women to depression, especially in relation to pituitary, thyroid and reproductive hormones.

The practice of hatha yoga and asanas has been found to be extremely effective in rectifying the situation. **(Muktananda S Nawa Yogini Tantra. 2004)**

Menstruation is dependent on the proper functioning of the chain made up of hypothalamus- pituitary-ovary and uterus. Pituitary hormones, follicle stimulating hormone (FSH), luteinizing hormones (LH), prolactin and thyroid hormones are required for normal development of ova and need to be investigated in cases of chronic anovulation, oligomenorhea and amenorrhea. **(Lobo RA 1999)**

It was inferred that after YogaNidra practice, patients acquired relief in heavy bleeding and irregular menstrual periods. As other research project, our study has some limitations.

The main limitation was that amenorrhea, dysmenorrhea, oligomenorrhea, polymen-orrhea, menorrhagia, metrorrhagia, and hypo menorrhea were included in the study all together. The sample size was not large enough to analyze the hypomenorrhic group and hypermenorrhic subgroups separately. The information of the menstrual cycle was based on the participant's self-reports not based on ultrasound scans; this is

also another limitation of the study. In future this study could be repeated in other populations with large number of patients. Further, some other yogic practices may be tried and compared with the present ones.

YogaNidra can be an effective practice to overcome the psychiatric morbidity associated with menstrual irregularities apart from bringing the hormonal profile towards normalcy. Therefore, Yogic relaxation training (YogaNidra) could be prescribed as an adjunct to conventional drug therapy for menstrual dysfunction. **(Yadav et al., 2016)**

YogaNidra is an effective technique, for physical or mental relaxation. Qualitatively YogaNidra is different from relaxation. It is a 'sleep' where all our burdens are removed in order to attain a more blissful state of awareness. Difference between YogaNidra and an ordinary sleep lies in intensity of a relaxation which is much more intense in YogaNidra than in ordinary sleep. Aim of YogaNidra is to focus the mind to achieve relaxation and increase Wellness. We used the YogaNidra technique, as mentioned in book YogaNidra by Swami Satyananda Saraswati. The final yoga classes conducted for 35 min per day, seven days a week for last two weeks.

Amita S et al., 2009 suggest that subjects on Yoga-nidra with drug regimen had better control in their fluctuating blood glucose and symptoms associated with diabetes, compared to those were on oral hypoglycaemics alone.

South East Asian countries have a highest burden of diabetes. In India the prevalence of diabetes is rising rapidly especially in the urban population because of increasing obesity and reduced physical activity. An objective of this study is to evaluate the

effect of Yoga-Nidra on blood glucose level in diabetic patients. (**Amita S et al., 2009)**

KhushbuRani et al.,2011 found significant improvement in pain symptoms (P<0.006), gastrointestinal symptoms (P<0.04), cardiovascular symptoms (P<0.02) and urogenital symptoms (P<0.005) after 6 months of YogaNidra therapy in Intervention group in comparison to control group, the results indicate that somatoform symptoms in patients with menstrual disorder can be decreased by learning and applying a program based on Yogic intervention (YogaNidra).YogaNidra appears to be a promising intervention for psychosomatic problems. It is cost-effective and easy to implement.

A randomized controlled trial observe the effect of YogaNidra practice on hormone levels in patients who had menstrual irregularities.YogaNidra practice was helpful in patientswith hormone imbalances, such as dysmenorrhea, oligomenorrhea, menorrhagia, metrorrhagia, and hypomenorrhea. **(Rani M et al., 2011)**

A significant positive effect was observed when yoga therapy was used as an adjunct in the patients of menstrual disturbances. There were significant improvements in the blood pressure, postural hypotension and sustained hand grip, heart rate expiration inspiration ratio and 30:15 beat ratios of the subjects after yogic practice. **(Monika et al., 2010)**

YogaNidra – Deep Relaxation

Deep relaxation may have substantial benefits on physical and psychological health. The relaxation response, a physiological phenomenon considered to be the opposite of the fight-or flight stress response, is of increasing interest in the medical field as a preventative and alternative treatment for stress-related disorders. Methods of inducing the relaxation response include some forms of yoga or meditation, progressive muscle relaxation, and stress management training. **(Rainforth et al., 2008)** The Relaxation Response Resiliency Program (3RP) is a standardized, 8-week program incorporating a variety of modalities to increase relaxation and resiliency. In a recent study, Stahl and colleagues (2015) found that a year-long intervention incorporating these various methods to increase the relaxation response, including yoga and meditation, decreased billable medical encounters by 43 percent. In addition to stress, researchers have suggested that relaxation may have positive effects on cardiovascular health **(Dusek et al., 2008)**, chronic pain **(Caudill et al., 1991)**, and menopausal symptoms. (**Irvin et al., 1996)**

The focus of the literature on the relaxation response is largely medical. However, relaxation has also been suggested as a potential preventative measure for burnout-related stress based on the ancient Tantric practice of nyasa, in which a mantra is repeated mentally at with concentration at specific parts of the body **(Saraswati, 1976)**. The yogic texts describe a state of consciousness called turiya, or the fourth state, which is a state of consciousness beyond waking, sleeping, and dreaming **(Saraswati, 1976, Birch & Hargraves 2015)**. This state is considered to lead to Samadhi, or bliss.Researchers have reported significant decreased in rage, anxiety,

and emotional reactivity **(Stankovic, 2011)**, increased joy and ability to manage stress, and increased sleep. **(Pence et al., 2014)**

YogaNidra may have positive effects in medical patients. Two studies have looked at the effect of YogaNidra on psychological and physiological symptoms associated with menstrual disorders and found significant positive results **(Rani et al., 2012, Singh et al., 2012)**.

A study by **(Pritchard et al., 2009)** examined the effects of YogaNidra on perceived stress levels in medical patients with cancer and multiple sclerosis and found the perceived stress was significantly reduced in the 12 participants after the 6-week program.

In a study by **Eastman-Mueller et al., 2013**, a sample of sixty-six college students participated in an 8-week YogaNidra intervention. Researchers assessed changes in worry and perceived stress. The data suggests that the intervention was helpful in reducing students' worry and stress.

There is evidence to suggest that yoga, meditation, and relaxation have positive effects on Participants were asked to complete a baseline assessment using the Perceived Stress Scale **(PSS-10; Cohen et al., 1983).** The PSS-10 is a widely used 10-item scale used to measure the degree to which events in one's life have been stressful, overwhelming, and unpredictable in the past month on a 0-4 Likert scale. It measures the perceived experience of stress, rather than objective variables that may contribute to increased stress. Participants were not asked about events in their life which may have contributed to stress, but rather the perceived experience of stress in

the last month. The PSS has been measured and tested effectively for reliability and validity. **(Cohen et al., 1983)**

The brain is the physical mediator of consciousness, linking mind, body and emotions into one harmonious unit. The neurosurgeon affects the body by stimulating the brain. The practitioner of YogaNidra begins at the other end of the nerve pathway by heightening the awareness of the body in order to stimulate the brain .The progressive movement of awareness through the parts of the body not only induces physical relaxation, but clears all the nerve pathways to the brain, but those governing the physical activity and those concerned with incoming information.

In addition to improving mood and decreasing stress, YogaNidra as a stress management intervention, appear in other populations to be capable of normalizing HPA axis regulation as well as lowering SNS activity. YogaNidra directed at better managing stress may be used to address the cortisol secretion abnormalities often present in PCOS women, especially since standard treatment with metformin does not appear to affect physiological responses to stress. If so, stress management approaches may also have the secondary effects of reducing hyperandrogenism, as has been demonstrated in women with other conditions. Much more research investigating the effectiveness of YogaNidra interventions among this population is needed, but this small study provides some evidence that these approaches are promising. Among the general population, interventions have helped individuals achieve changes such as reductions in BMI, percent fat, waist circumference, lipids, and caloric intake.

4. METHODOLOGY

MATERIALS AND METHODS

Study design : Experimental pre post study

Study population:

40 PCOS women of age group between 18 -35 years, who attend the Government Yoga & Naturopathy Medical College Hospital outpatient department, Arumbakkam, Chennai -106, will participate in the study. (The diagnosis of PCOS was based on the Rotterdam criteria 2003 and inclusion criteria of this study).

After explaining the purpose of this study & obtaining informed written consent, a detailed case history and clinical Examination will be performed to the patients.

Ethical committee clearance:

Clearance from the Institutional ethical committee was obtained prior to the conduction of the study.

Informed consent:

Informed consent from the participants was obtained after explaining the protocol and benefits to them.

Selection of the subjects:

Inclusion Criteria

1. Those who satisfied the Rotterdam Criterion for PCOS will be included in the study.

2. Women with PCOS under any treatment.

3. Those who satisfied the Cohen-perceived stress scoring.

Exclusion Criteria

1. Pregnancy

2. Woman who were using oral contraceptives / hormone treatment/insulin-sensitizing agents/ ovulation induction agents within previous 6 months.

3. Woman who were practicing yoga from a month or more.

4. Thyroid dysfunctions

5. Conditions that mimic PCOS like ovarian hyperthecosis, congenital adrenal hyperplasia, and Idiopathic hirsutism

6. Subjects with neoplastic, hepatic, respiratory and any cardiovascular disorder or other medical illness (i.e. respiratory and heart failure and renal disease)

Data collection and Analysis:

1. Anthropometric Measurements - Height, Weight, BMI, Waist-Hip Measurement and ratio

2. Blood Glucose - OGTT, HBA1C, FBS, PPBS

3. Lipid Profile - TOTAL CHOLESTEROL, LDL, HDL, TGL

Analysis Plan : Paired Student‘t’ test, R statistical free software version 3.2.0

Study questionnaire:

Cohen-perceived stress scoring.

Modified Ferriman - Gallwey scoring system (Ferriman D and Gallwey J 1961)

History of reproductive illnesses was obtained by using CRF.

Measurement of the anthropometric indices:

Standing height: Measuring tape was used to measure the standing height in centimeters.

Weight: Weight as recorded in kilograms using the portable weighing machine.

Body Mass Index: BMI was calculated by using the formula.

BMI= weight (in kg)/ht in meter^2 (Quetelet index)

Anthropometric measurements included a waist circumference in centimeters measured at the narrowest circumference, midway between the upper border of iliac crest and the lower rib margin, whereas the hip circumference was taken as the widest measurement at the level of the greater trochanter with subject was standing and breathing normally. (To rule out abdominal type obesity, which are characteristics for PCOS women)

Height was recorded in centimeters and weight in kilograms.

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m). Overweight was defined as a BMI between 25.0 and 29.9, and obese as 30.0 or higher according to World Health Organization categories.

HIRSUTISM

Clinical hyperandrogenism

Hirsutism was assessed by Ferriman Gallwey score of ≥8 over 9 body parts.

Hirsutism is evaluated using a modified Ferriman–Gallwey scoring system. (Ferriman D and Gallwey J 1961) This tool is used to evaluate hair growth at seven sites: upper lip, chin/face, chest, back, abdomen, arms, and thighs. A score of 0 is given in the absence of terminal hair growth and a score of 4 is given for extensive growth.A total score of 8 or more is indicative of hirsutism. (Unluhizarci K et al., 2012) criteria

ROTTERDAM CRITERIA

The diagnosis was based on the 2003 Rotterdam consensus (the Rotterdam European Society for Human Reproduction and Embryology (EHSRE)/American Society for Reproductive Medicine (ASRM) – sponsored PCOS consensus workshop group) with at least two of the following features:

(i) oligo-ovulation or chronic anovulation, amenorrhea

Oligo-ovulation and/or anovulation was characterized by oligomenorrhea (intermenstrual intervals of ≥35 days) and amenorrhea (intervals >3 months).

(ii) Clinical and/or biochemical hyperandrogenism, and

(iii) Ultrasound appearance of polycystic ovaries.

A standard questionnaire was used to document length of menstrual cycles; personal, medical, and family history of diabetes; hypertension; obesity;

and ischemic heart disease. Signs of androgen excess (hirsutism, acne, and alopecia) and insulin resistance were noted in the physical examination.

BLOOD PRESSURE CHECK UP

Sitting blood pressure was measured after a 5-min rest using a standard sphygmomanometer.

BIOCHEMICAL INVESTIGATION

Overnight fasting blood sample and a 75 g oral glucose tolerance test was obtained in all women. Impaired fasting glucose, impaired glucose tolerance test, and diabetes were defined in accordance with the American Diabetes Association revised definition.

After 10-12 hours of overnight fasting, blood sample (5 ml) will be taken for

OGTT - Glucose oxidase peroxidase method

HbA1C - HPLC

FBS, PPBS

LIPID PROFILE

Total cholesterol - Cholesteroloxidase peroxidase method (Photometry, Enzymatic)

HDL Direct - Polyethylene Glycol precipitation method

LDL Direct - Poly vinyl sulfonic acid (precipitation method)

TGL - Glycerol phosphate oxidase method

The samples were stored at -20 ° C until it is used for estimating the Blood glucose and Lipid profile.

The 40 PCOS individuals selected and did YogaNidra for 40 minutes over a period of 3 months. At the end of 12 weeks, re-estimation of Blood glucose, Lipid profile, Blood pressure and re-evaluation BMI and Waist hip ratio was done.

5. RESULTS

Table.4: Anthropometric parameters of the study participants

Variables	Mean±SD
Age	26.13±5.30
Height	155.6±4.17
Weight	74.59±12.97
BMI	30.75±4.75

Table.1 showed the anthropometric parameters of the study participants. Mean average of the subject was 26.13 yrs with height of 155.6 cm and weight about 74.59 kg. The Mean BMI was 30.75 kg/m^2.

Table.5: Effect of YogaNidra practice on

Resting Cardiovascular parameters

Variables	Before	After	P value
Weight	74.59±12.97	70.25±12.14	**0.001**
BMI	30.75±4.75	28.92±4.44	**0.001**
Waist hip ratio	0.84±0.03	0.80±0.02	**0.02**
SBP	128.70±8.46	122.0±9.26	**0.0001**
DBP	78.42±6.42	72.0±8.72	**0.0001**

SBP - Systolic blood pressure,

DBP - Diastolic blood pressure,

BMI - Body mass index.

After YogaNidra Heart rate, SBP and DBP reduced significantly

(P<0.001) after yoga nidra showed the parasympathetic

domination over sympathetic nervous system.

Table.6: Effect of YogaNidra practice on

Blood Glucose in PCOS subjects

	Before	**After**	**P value**
FBS	90.70±13.54	83.08±10.97	**0.001**
PPBS	129.5±14.23	113.3±13.25	**0.001**
HbA1C	5.68±0.68	5.06±0.42	**0.0001**

Data Expressed Mean±SD.

After YogaNidra, there was a significant (P <0.001) improvement

was in the subjects especially

FBS from 90.70±13.54 to 3.08±10.97

PPBS from 129.5±14.23 to 113.3±13.25

HbA1C (5.68±0.68vs5.06±0.42)

Table.7: Effect of YogaNidra practice on

GTT in PCOS subjects

	Before	**After**	**P value**
GTT1	145.0±14.07	127.5±25.25	**0.0001**
GTT2	147.2±27.68	135.8±23.60	**0.0001**
GTT3	135.3±25.33	125.3±22.53	**0.0001**
GTT4	124.6±17.81	112.6±16.83	**0.0001**

Data Expressed Mean±SD.

After YogaNidra, there was a significant (P <0.0001) improvement was in the subjects especially

GTT1 from 45.0±14.07 to 127.5±25.25.

GTT2 from 147.2±27.68 to 135.8±23.60

GTT3 from 135.3±25.33 to 125.3±22.53

GTT4 from 124.6±17.81 to 12.6±16.83

Table.8: Effect of YogaNidra practice on Lipid profile in PCOS subjects

	Before	**After**	**P value**
Cholestrol	177.7±32.61	165.8±32.08	**0.001**
Triglycerides	132.9±30.44	118.2±22.09	**0.001**

Data Expressed Mean±SD.

After YogaNidra, there was a significant (P <0.001) reduction was

There among the lipid profile variables in the subjects as below,

Cholestrol from 177.7±32.61 to 165.8±32.08

Triglycerides from 132.9±30.44 to 118.2±22.09

Table.9: Effect of YogaNidra practice on Lipid profile in PCOS subjects

	Before	**After**	**P value**
HDL	39.23±7.27	43.55±6.61	**0.0001**
LDL	119.1±29.11	101.1±30.56	**0.0001**
VLDL	26.70±6.25	28.65±5.61	**0.0001**

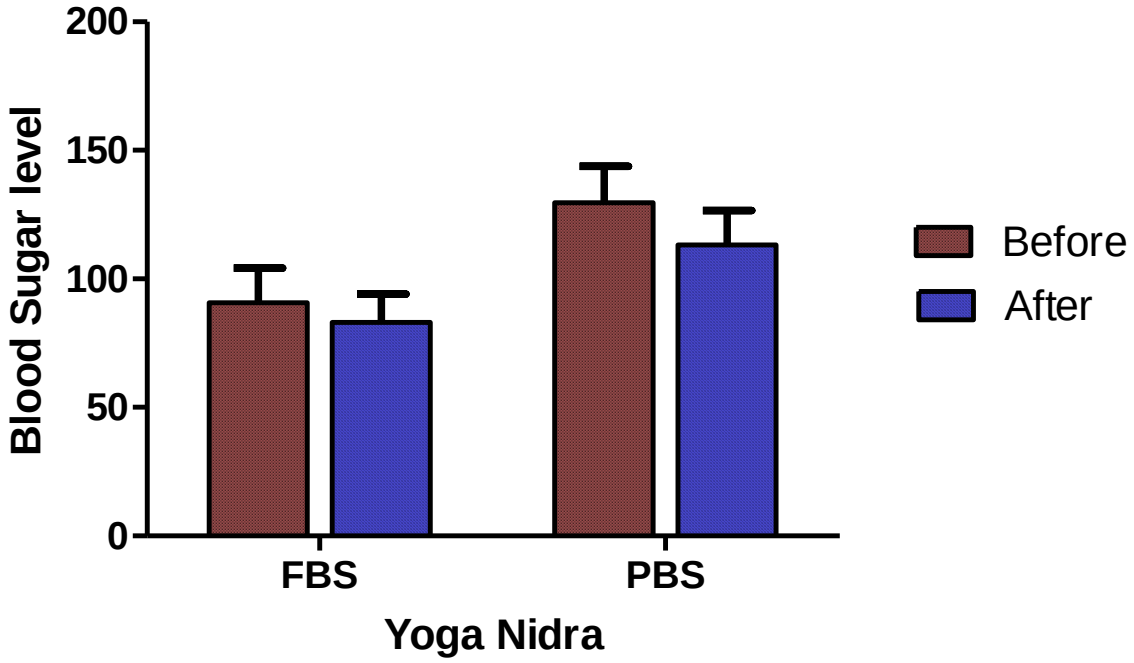
After YogaNidra, there was a significant (P <0.0001) reduction was

there among the lipid profile variables in the subjects as below

LDL from 119.1±29.11 to 101.1±30.56

VLDL from 26.70±6.25 to 28.65±5.61

HDL from 39.23±7.27 to 43.55±6.61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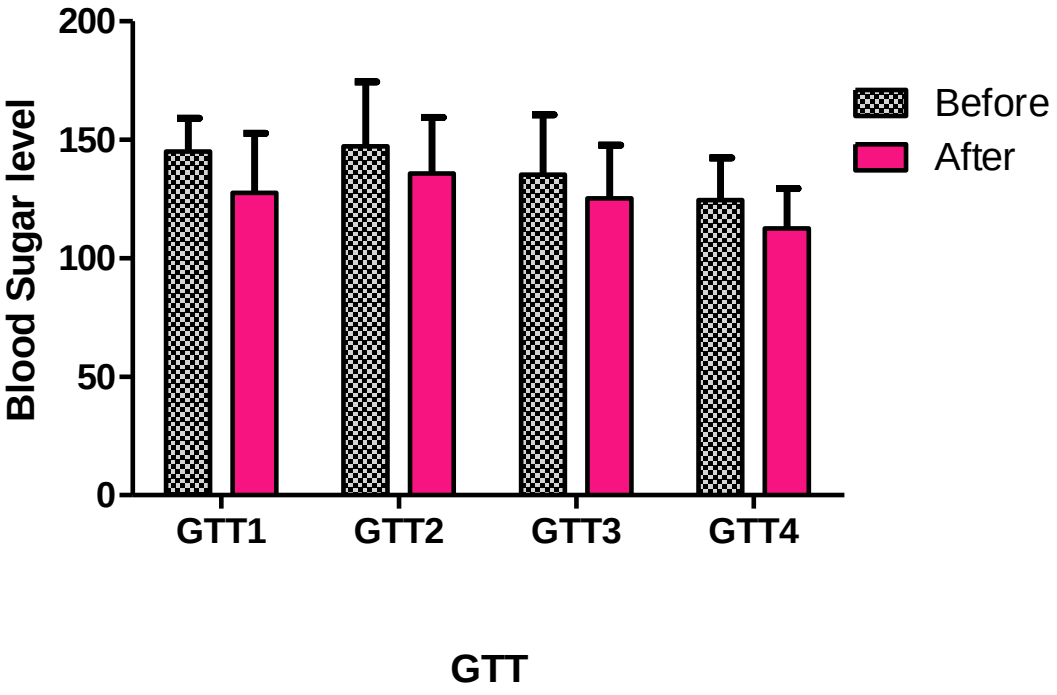
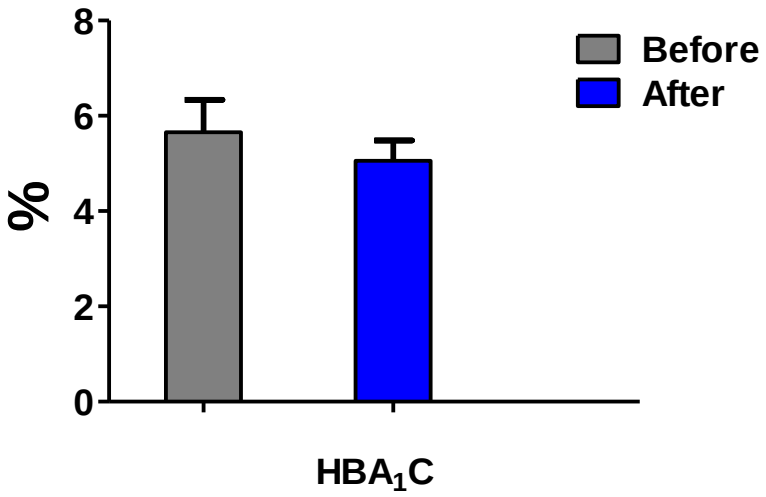
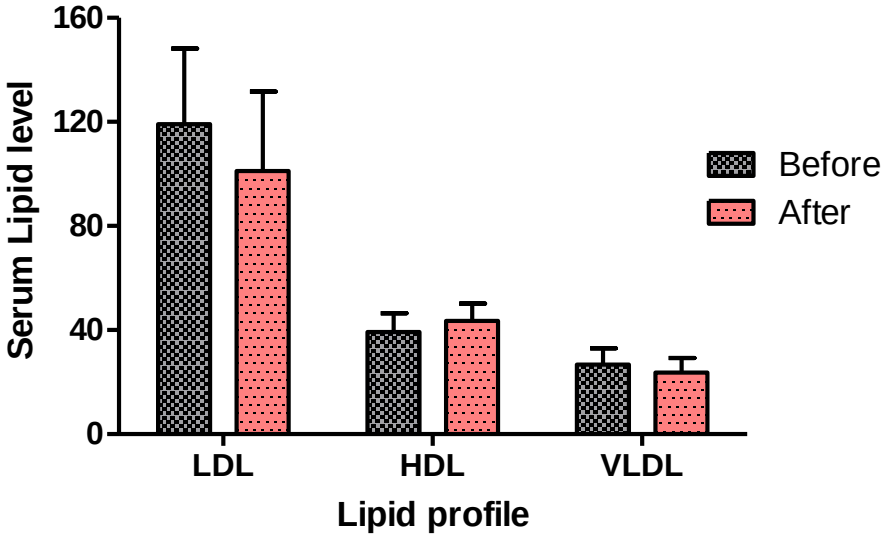
150
100
50
0
Blood Sugar level
FBS
PBS
Yoga Nidra
Before
After


200
150
100
50
0
Blood Sugar level
GTT1
GTT2
GTT3
GTT4
GTT
Before
After


8
6
4
2
0
%
Before
After
HBA1C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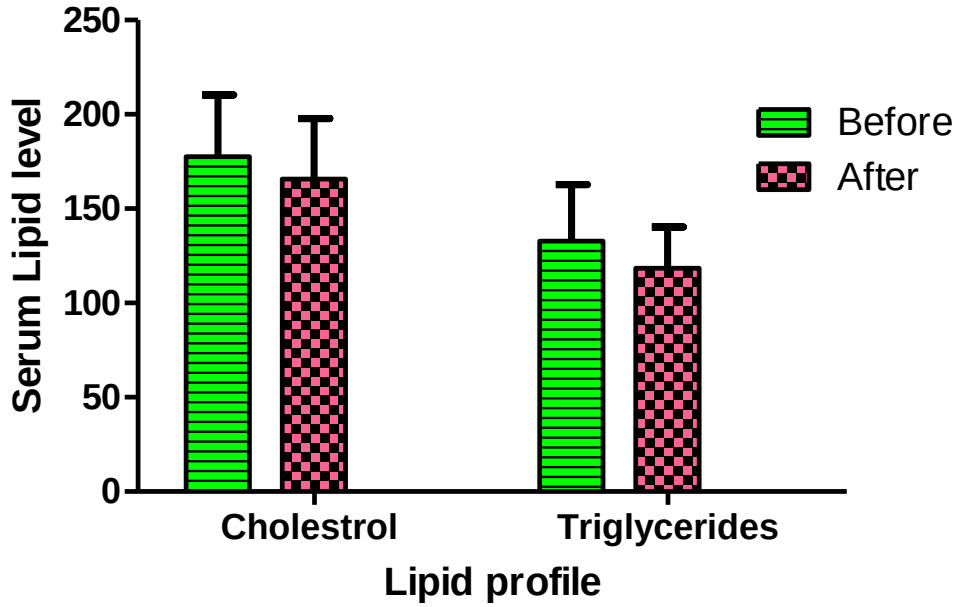
120
80
40
0
Serum Lipid level
Before
After
LDL
HDL
VLDL
Lipid profile


250
200
150
100
50
0
Serum Lipid level
Before
After
Cholestrol
Triglycerides
Lipid profile

6. DISCUSSION

In this study after YogaNidra, there was a significant (P <0.001) reduction was seen in the subjects especially FBS from 90.70±13.54 to 3.08±10.97, PPBS from 129.5±14.23 to 113.3±13.2, HbA1C (5.68±0.68vs5.06±0.42) and there was a significant (P <0.0001) reduction was in the subjects especially GTT1 from 45.0±14.07 to 127.5±25.25 GTT2 from 147.2±27.68 to 135.8±23.60 GTT3 from 135.3±25.33 to 125.3±22.53 GTT4 from 124.6±17.81 to 12.6±16.83

In this study after YogaNidra heart rate, SBP and DBP reduced significantly (P<0.001) showed the parasympathetic domination over sympathetic nervous system.

In this study there was a significant (P <0.001) reduction in the subjects among the lipid profile variables Cholestrol from 177.7±32.61 to 165.8±32.08, Triglycerides from 132.9±30.44 to 118.2±22.09 and also significant (P <0.0001) reduction among the lipid profile variables LDL from 119.1±29.11 to 101.1±30.56, VLDL from 26.70±6.25 to 28.65±5.61, HDL from 39.23±7.27 to 43.55±6.61 in the subjects.In this YogaNidra intervention, there was a significant (P <0.0001) reduction among the Anthropometric parameters in the subjects, weight from 74.59±12.97to 70.25±12.1**,** BMI from 30.75±4.75 to 28.92±4, waist hip ratio from 0.84±0.03 to 0.80±0.02

PCOS Women possible to show evidence of exaggerated SNS and defect in HPA-axis, signifying that YogaNidra will improve the coping up of stress , positive attitude including stress management interventions to regulate the HPA

axis **(Antoni MH et al., 2000, Cruess DG et al., 2000, Phillips K et al.,2008)** as well as lowering SNS activity **(Antoni MH et al .,2001)**

Techniques like relaxation and cognitive behavioral therapy will reduce stress may be used to address the cortisol secretion abnormalities often present in PCOS women, especially metformin does not appear to affect physiological responses to stress. **(Benson S et al., 2009)** Stress management intervention might have the secondary effects of reducing hyperandrogenism that is demonstrated in women with other conditions **(Cruess D et al., 2001)**

Very little research has employed cognitive behavioral therapy (CBT) or other psychological interventions among women with PCOS. The only such study published to date is a pilot study conducted among adolescents with PCOS **(Rofey DL et al., 2009)**

8-week CBT intervention resulted in significant decreases in weight and depressive symptoms and significant improvements in menstrual regularity and sleep-related breathing. This study shows some evidence that these approaches are promising.Among the general population; CBT interventions have helped individuals to achieve reductions in BMI, percent fat, waist circumference, lipids, and caloric intake**. (Mefferd K et al., 2007, Vignolo M et al., 2008, Ash S et al., 2006)**

Significant improvement in anxiety scores after Yoga Nidra intervention following meditation. **(Eppley KR et al., 1989) and breathing exercises (Brown RP and Gerbarg PL 2005)** In anxiety state, increased response of hypothalamus and

increased sympathetic activity. YogaNidra appears to regulate hypothalamus, in a way resulting in decreased sympathetic (excitatory) nervous activity and increased parasympathetic (inhibitory) function. **(Satyananda SS. Yoga nidra. 2009)**

YogaNidra intervention gave a significant decrease in depressive symptoms (according to the psycho-biological general wellbeing Index).Previous studies have also shown that using yoga interventions inother conditions (cancer survivors, self-reported emotional distress), found to be effective in depressive and mood symptoms, as well as anxiety and physical well-being. **(Michalsen A et al., 2005)**

Significant improvement in positive wellbeing, general health and vitality in intervention group. YogaNidra is believed to balance psychic and vital energies within the psychic channels (Nadis) of the energy framework underlying the physical body.

Free flow of these energies is considered to be the basis of optimal physical and mental health. Findings from other studies also are in line with present study. **(Basavaraaddi IV et al., 2008, Kiecolt-Glaser Jket al., 1992, Strijk JE et al., 2009)**

Previous studies have found significant improvement in self-esteem with Yogic exercises. **(Benavides S et al., 2008)**

YogaNidra intervention program decreased depressed mood, feelings of guilt, insomnia, genital problems, tension, fear and anxious mood which are symptoms included as items of PGWBI. Tsunami survivors of the Andaman Islands was a

significant decrease in self rated fear, anxiety, sadness and disturbed sleep, respiratory and heart rate was also significantly improved.**(Telles S et al.,2007)**

Significant change in TSH, FSH, LH, and Prolactin levels, also metabolic effects of meditation (Yoga Nidra) includes a decreased adrenocortical activity, long term decreased cortisol secretion and lesser thyroid stimulating hormone (TSH) abnormalities. **(Schell FJ et al., 1994)**

Metabolic effects of meditation (Yoga Nidra) includes a decreased adrenocortical activity, long term decreased cortisol secretion and decreased thyroid stimulating hormone (TSH). Imbalances in the hormonal profile also predispose women to depression, especially in relation to pituitary, thyroid and reproductive hormones**. (Muktananda S. Nawa Yogini Tantra 2004)**

Menstruation is dependent on the proper functioning of the chain made up of hypothalamus- pituitary-ovary and uterus.Pituitary hormones, follicle stimulating hormone (FSH), luteinizing hormones (LH), prolactin and thyroid hormones are required for normal development of ova and need to be investigated in cases of chronic anovulation oligomenorhea and amenorrhea, after Yoga Nidra practice, patients acquired relief in heavy bleeding and irregular menstrual periods.

Imbalances in the hormonal profile also predispose women to depression, especially in relation to pituitary, thyroid and reproductive hormones.

Yoga Nidra is believed to balance psychic and vital energies within the psychic channels (Nadis) of the energy framework underlying the physical body. The

practice of hatha Yoga Nidra has been found to be extremely effective in rectifying the situation.

Depending on the symptom, patient seeks treatment.Clomiphene has shown the best results in treating infertility, whereas data are limited regarding the pharmacological treatment of androgenic symptoms. Long-term consequences of PCOS, which include type-2 diabetes and cardiovascular disease, can be treated with antidiabetic drugs and statins. **(Uche Anadu Ndefo et al., 2013)**

Nonpharmacological Approaches because the primary cause of PCOS is unknown, treatment is directed at the symptoms. Few treatment approaches improve all aspects of the syndrome, and the patient's desire for fertility may prevent her from seeking treatment despite the presence of symptoms. **(Legro RS 1998)**

Treatment goals have to include regulating anovulation, inhibiting the action of androgens on target tissues, and reducing insulin resistance. Weight reduction for obese patients with PCOS is beneficial in many ways. Weight loss helps to decrease androgen, luteinizing hormone (LH), and insulin levels. It also helps to regulate ovulation, thereby improving the potential for pregnancy. **(Guzick DS 2004)**

As a safe and effective a non pharmacological mode of intervention, yoganidra can be utilized for polycystic ovarian syndrome justified by the cost effective and availability of yoga in all over the world and YogaNidra being concurrently effective and effortless practice, can be practiced by everyone, even morbidly obese and those who are having movement constraint or of limited physical

activity.Subjects had significant result in weight reduction, effective management in long-term consequences of PCOS such as DM and cardiovascular diseases through regulating their blood sugar level and lipid profile to normal and also regulating sympathetic activity and HPA axis by coping stress in an effective way. This furthers the scope of expanding the research more concretely in the direction of non pharmacological mode of treatment for PCOS with a larger sample size.

Pharmacologic versus a psychological intervention approach in the management of PCOS a very reasonable question is: Why we need a psychological intervention in lieu of a pharmacological intervention, such as prescribing metformin to women with PCOS? **(Blackburn IM and Moore RG 1997, Fava GA et al., 1998, Gould RA et al., 1995)**

In the management of PCOS treatment include behavioral and psychological interventions as adjunctive to standard medical care.It is very likely that clinicians already employ behavioral and psychological interventions (e.g., smoking cessation advice, addressing barriers to adherence, brief assessment of mood) in the absence of established guidelines. Research protocols could help establish whether these interventions are indeed effective in managing this chronic disorder.

Given the evidence supporting relationships among physiological and psychological characteristics common in PCOS, and the existence of behavioral and/or psychological intervention approaches that result in improved metabolic, anthropometric, and reproductive parameters, some aims for future research might include the following:

• Investigate whether improvement in sleep quality specifically, reduction in sleep apnea among women with PCOS reduces not only physiological abnormalities such as visceral fat and inflammation but also improves other characteristics such as mood and ovulation rate.

• Since muscle contractions stimulate glucose uptake in the absence of insulin and increased soleus muscle mass may reduce insulin resistance, future work should test whether yoga increases muscle mass and reduces insulin resistance in young women with PCOS.

• Elucidate the behavioral and interpersonal goals that might motivate an adolescent who is newly diagnosed with PCOS to improve her lifestyle to achieve weight loss (via naturopathy and yogic management).

Limitations:

- USG can be done to assess the morphological changes among the PCOS patients for the impact of the YogaNidra.
- Oxidative stress markers level along with lipid profile will be more ideal for assessing the effect of YogaNidra on PCOS.
- Bio markers (Cortisol and amylase) level will be measured.
- Large sample size with proper study design such as Randomized control trial will be more appropriate study design to evaluate the impact of YogaNidra.

7. SUMMARY AND CONCLUSION

PCOS is a common and chronic endocrine disorder characterized by hyperandrogenism, menstrual cycle abnormalities and polycystic ovaries and common cause of infertility and pregnancy complications. Development of PCOS appears to be spurred by a chronic state of insulin resistance cause defect in HPA axis and ovarian abnormalities that are likely `programmed to be dysfunctional very early in life. Increased insulin resistance is linked with decreased SHBG, consequences in increased bioavailable testosterone. Increased testosterone causes infertility and increased acne, alopecia, and hirsutism, and it also appears to be associated with an increased inflammatory state, mood disorders, and obesity.

Women with PCOS also have a tendency to show signs of central obesity and increased visceral fat compared with non-PCOS women matched for BMI. This phenomenon could be due to an HPA axis defect such that women with PCOS have increased or abnormal cortisol responses to physical and psychological stressors. Central obesity alone does not fully explain the presence of insulin resistance or inflammation, as even lean women with PCOS show indication of insulin resistance and increased inflammatory markers, suggesting that these maladaptive physiological states are inherent among women with PCOS. Embarrassing PCOS symptoms such as acne, hirsutism, and central obesity appear during adolescence and significantly affect the well-being and mental health of the young woman during a phase in life in which she is expanding her social network and beginning to date.

PCOS alone and possibly appearance of its symptoms set the stage for development of emotional disturbances such as depression and social phobia. These emotional difficulties may, in turn, exacerbate already-existing obesity and other maladaptive physiological characteristics increased consumption of carbohydrates, smoking, reduced exercise) and physiological pathways, as previously discussed.Physiological and psychological abnormalities are more in women with PCOS are strongly interconnected.

These relations suggest that management of PCOS would benefit significantly from inclusion of psychological and or behavioral approaches and stress management intervention through higher stage of yoga that is YogaNidra (a form of prathyahara).This review presented the evidence supporting the robust relationships between physiological and psychological processes and physical and emotional symptoms in women with PCOS. To ease emotional disturbances might result in enhanced physiological processes with the result of improving insulin resistance, HPA axis functioning, obesity, and hyperandrogenism consequently, via the psychological-physiological pathways described hyperandrogenemic symptoms of PCOS might be alleviated, and the incidence and exacerbation of PCOS and its symptoms, especially among adolescents and also the long term consequences of PCOS.

The present study suggests that YogaNidra can be safely and effectively used in the treatment of Polycystic ovarian syndrome justified by the cost effective and availability of yoga in all over the world and YogaNidra practice being concurrently effective and effortless, it can be practiced by everyone, even

morbidly obese and those who are having movement constraint or of limited physical activity.

Subjects had significant result in weight reduction, effective management in long-term consequences of PCOS such as DM and cardiovascular diseases through regulating their blood sugar level and lipid profile to normal and also regulating sympathetic activity and HPA axis by coping stress in an effective way.

As YogaNidra concurrently address the mind and body it may be possible to attain the results safe and positive in a short span of time as a non - pharmacological intervention which deals with and recover all aspects of the syndrome assertively.

Hence YogaNidra would be very much recommended as an effectual therapy which could replace rather than as an adjuvant with the available line of pharmacological management as PCOS women need long term treatment.

This furthers the scope of expanding the research more concretely in the direction of non pharmacological mode of treatment for PCOS with a larger sample size.

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9. ANNEXURES

	PERSONAL INFORMATION	
1.	Name	
2.	Age	
3.	Date of Birth	
4.	Address	
5.	Contact no	
	ANTHROPOMETRIC MEASURES	
6.	Height (meters)	
7.	Weight (kilogram)	
8.	BMI (kg/m2)	
9.	Waist (centimeters)	
10.	Hip (centimeters)	
11.	Waist : Hip Ratio	
	CLINICAL SYMPTOMS	
12	Years since diagnosis	
13	Cycle Characteristics	Oligomenorrhea? Longest Amenorrhea?
14	Acne	Sites:

		Grade: ◯ Mild◯ Moderat◯ Severe
15	Alopecia	Grade: ◯ Mild◯ Moderat◯ Severe
16	Hirsutism	Lip _____ Chin _____ Chest _____ Upper Abdomen _____ Lower Abdomen _____ Arms _____ Thighs _____ Upper Back _____ Lower Back _____ TOTAL _____

INFORMED CONSENT FORM

Title of the study: "Evaluation of effect of YogaNidra on biochemical changes in Polycystic ovarian syndrome women between the age of 18-35 years.""

Name of the Participant:

Name of the Principal Investigator: Dr.A.Vanitha

Name of the Institution:

Government Yoga and Naturopathy Medical College (GYNMC)

Arumbakkam, Chennai - 600106

Documentation of the informed consent

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in "**Evaluation of effect of YogaNidra on biochemical changes in Polycystic ovarian syndrome women between the age of 18-35 years."**

1. I have read and understood this consent form and the information provided to me.

2. I have had the consent document explained to me.

3. I have been explained about the nature of the study.

4. I have been explained about my rights and responsibilities by the investigator.

5. I have been informed the investigator of all the treatments I am taking or have taken in the past _____ months including any native (alternative) treatment.

6. I have been advised about the risks associated with my participation in this study.

7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.

8. I have not participated in any research study within the past _____month(s).

9. I am aware of the fact that I can opt out of the study at any time without having to give

any reason and this will not affect my future treatment in this hospital.

10. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent.

12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.

13. I have understood that my identity will be kept confidential if my data are publicly presented.

14. I have had my questions answered to my satisfaction.

15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

For adult participants:

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____ Signature_____

Date_____

Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____

Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____

Date_____

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆய்வு தலைப்பு : ----------

ஆராய்ச்சியாளர் பெயர் : மரு.ஆ.வனிதா

ஆராய்ச்சி நடக்கும் இடம்:

பங்கு பெறுபவரின் பெயர்: வயது:

பாலினம்: ஆண் / பெண்

பங்கு பெறுபவரின்அடையாள எண்

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கமும்

முழுமையாக தெளிவாக எனக்கு விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட தகவல்களை புரிந்து கொண்டு நான் எனது

சம்மதத்தைத் தெரிவிக்கிறேன்.

நான் மேற்குறிப்பிட்ட ஆராய்ச்சியில் பங்குபெற்று பரிசோதனை

மேற்கொள்ளவும் முழு சம்மதம் தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் இருந்து நான் எந்த நேரமும் பின்வாங்கலாம் என்றும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் புரிந்து கொண்டேன்.

நான் யோகநித்ரா ஆராய்ச்சியின் தகவல்களை பெற்று கொண்டேன்.

நான் என்னுடைய சுயநினைவுடனும்முழு சம்மதத்துடனும் ஆராய்ச்சியில் என்னை பரிசோதிக்க சம்மதிக்கிறேன்.

ஆராய்ச்சியாளர் கையொப்பம்: பங்கு பெறுபவர் கையொப்பம் /

தேதி: இடதுகை பெருவிரல் ரேகை

ஆராய்ச்சி தகவல் தாள்

ஆய்வு தலைப்பு :

பங்கு பெறுபவரின் பெயர்: வயது:

பாலினம்: ஆண் / பெண்

பங்கு பெறுபவரின்அடையாள எண்:

அரசு யோகா மற்றும் இயற்கை மருத்துவ கல்லூரி மருத்துவமனையில் யோகநித்ரா பயிற்சியின் மூலம் சினைப்பை நீர்கட்டிகளுடைய மகளிர் உடலில் ஏற்படும் உயிர்வேதியியல் மாற்றங்களை அறியும் ஆராய்ச்சி இங்கு நடைப்பெறுகிறது.

யோகநித்ரா பயிற்சி மனித உடலில் ஏற்படுத்தும் மாற்றங்களை அறிவதன் மூலம் ,சினைப்பை நீர்கட்டிகளுடைய (PCOS) மகளிர் உடலில் அந்நோயினால் ஏற்படும் நீண்ட நாள் பாதிப்புகளான சர்க்கரை நோய் மற்றும் இருதய நோய் பாதிப்புகளிலிருந்து மகளிரை காக்க இயலும் .நீங்கள் இந்த ஆய்வில் பங்கேற்று ஒத்துழைப்பு நல்கிட

நாங்கள் விரும்புகிறோம். இதில் உங்களுடைய ரத்த சர்க்கரை அளவு , உடல் நிறை குறியீடு எண், நாடி, ரத்த அழுத்தம் பரிசோதிக்கப்படும். இதனால் தங்களுடைய அன்றாட செயல்பாடுகள் பாதிக்கப்படாது என்று தெரிவித்துகொள்கிறோம்.

முடிவுகளையும் கருத்துகளையும் வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்கள் பெயரையோ அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகள் ஆராய்ச்சியின் போது அல்லது அதன் முடிவில் அறிவிக்கப்படும் என்பதையும் தெரிவித்து கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் ஆகும்.மேலும் நீங்கள் இந்த ஆராய்ச்சியில் இருந்து எந்த நேரமும் பின்வாங்கலாம் என்பதை தெரிவித்து கொள்கிறோம்.

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