EVALUATION OF EFFECT OF YOGA ON AUTONOMIC FUNCTIONS AND ADRENAL FATIGUE IN POLYCYSTIC OVARIAN SYNDROME

Dissertation submitted to

The Tamil Nadu DR. MGR Medical University

In partial fulfilment of the regulations for the award of the degree of

M.D. PHYSIOLOGY

INSTITUTE OF PHYSIOLOGY & EXPERIMENTAL MEDICINE

Madras Medical College and Rajiv Gandhi Government General Hospital

CHENNAI –600003

THE TAMIL NADU DR. MGR MEDICAL UNIVERSITY

CHENNAI –600032

APRIL 2017

CERTIFICATE

This is to certify that the dissertation entitled **"EVALUATION OF EFFECT OF YOGA ON AUTONOMIC FUNCTIONS AND ADRENAL FATIGUE IN POLYCYSTIC OVARIAN SYNDROME"** by the candidate **Dr. K.NATHIYA** for M.D Physiology is a bonafide record of the research done by her during the period of study (2014 –2017) in the Institute of Physiology and Experimental Medicine, Madras Medical College, Chennai –600003.

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ACKNOWLEDGEMENT

There is hardly any task than acknowledging my gratitude to all those who have helped me in so many ways during my course.

I gratefully and sincerely thank **Dr. M.K. MURALI THARAN, M.S. Mch.,** the Dean of Government Madras Medical College and Hospital, Chennai for granting me permission to carry out the study at the Institute of Physiology and Experimental Medicine, Madras Medical College and Hospital.

I will forever be thankful to **PROF. Dr. C.THIRUPATHI, M.D.,** Director of Institute of Physiology and Experimental medicine, Madras Medical College, Chennai for providing insightful discussions about the research and giving me the opportunity to develop my own individuality and allowing me to work with such independence.

I will forever be thankful to **PROF. Dr. K.PADMA M.D.,** Former Director and Head of Institute of Physiology and Experimental medicine, Madras Medical College, Chennai for the scattered ideas and concepts at the outset of this thesis work could be completed because of the watchful and in-depth guidance

I am thankful to **PROF. Dr. A.PARIMALA, M.D.,** Professor, Institute of Physiology and Experimental medicine, Madras Medical College, Chennai for her guidance, motivation, thoughtful criticisms, supported me with love & care.

I am extremely thankful to **PROF. Dr. P.SATHYA, M.D.,** Professor, Institute of Physiology and Experimental medicine, Madras Medical College, Chennai, for her care and advice during the study period.

I am thankful to **PROF. Dr. R.VIJAYALAKSHMI, M.D.,** Professor, Institute of Physiology and Experimental medicine, Madras Medical College, Chennai, for her support during throughout this study period.

I am thankful to **Dr.SRIPRIYA**, Assistant Professor, Department of medical endocrinology, Rajiv Gandhi Government General Hospital, Chennai, for providing me the subjects needed for the study.

I am extremely grateful to **Dr. S.T. VENKATESHWARAN M.D., Professor and Head of Department**, Department of Yoga and Naturopathy, Government Yoga & Naturopathy Medical College Arumbakkaam Chennai for his guidance and support.

I would especially like to thank **Dr. K. AANANDHA SUBRAMANIAM, M.D., and Dr. GOWRI.V** Assistant Professors, Institute of Physiology and Experimental Medicine, Madras Medical College, Chennai for their unconditional help and guidance throughout my course.

I sincerely thank **Dr. M. JANET SUGANTHA, M.D., Dr. T.N. VIJAYALAKSHMI, M.D., Dr. SHANTHIMALAR, M.D., Dr. S. KAVITHA, M.D., M,D., Dr.INDHUMATHI, M.D., Dr. SYED SAFINA, M.D., Dr. ANITHA PONMALAR.,** Assistant Professors, Institute of Physiology and Experimental Medicine, Madras Medical College, Chennai for their advice, time and attention.

I immensely thank **Dr.VENKATESHWARAN. A.R**. Professor and Head of the Department, Department of Medical Gastroenterology, Stanley

Medical College, Chennai for the assistance and willingness to discuss ideas at all stages which helped me for the successful completion of the thesis work.

I am thankful to **Dr.AMBIKA,** Department of Yoga and Naturopathy, Lifestyle and wellness clinic, Madras Medical College, Chennai

I am thankful to **Dr.VANITHA & Dr. PANDIYARAJAN, Dr. SRIDEVI,** postgraduates, Department of Yoga and Naturopathy, government yoga and naturopathy college, Arumbakkam.

I thank all the staff members and technicians, **Institute of Physiology**, Madras Medical College, Chennai for their support and cooperation throughout this study.

I thank all the staff of **Institute of Biochemistry,** Madras Medical College for their laboratory and technical support and allowing me to do Lab tests in their Institute.

I thank all my subjects for being an essential part of this research and making it a success.

I am thankful to my senior **Dr. CHARUMATHI.V M.D.,** for her immense help throughout my study period.

I feel immensely grateful to my colleagues, all my friends and especially my seniors who have been with me from the start of this course for the support.

Last but not Least I am very thankful to my Parents, my sister and her husband and my brother for their unconditional love, support and care.

Above all I thank God Almighty for blessing this endeavour.

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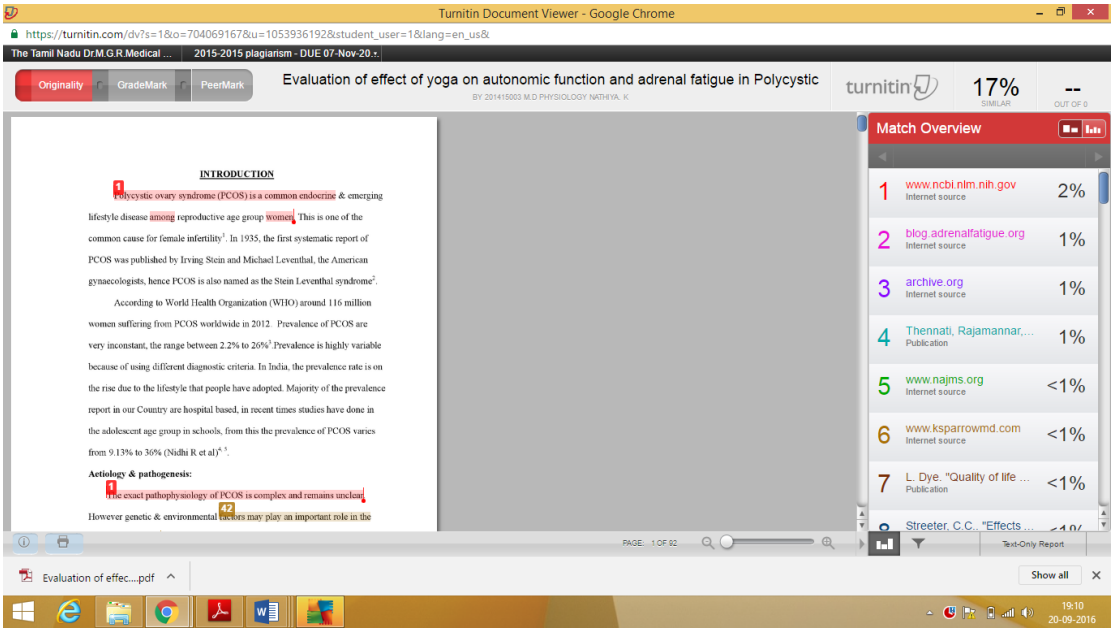
ABBREVIATIONS

PCOS	PolyCystic Ovarian Syndrome
WHO	World Health Organization
HPA axis	Hypothalamo Pituitary Adrenal axis
HPO axis	Hypothalamo Pituitary Ovarian Axis
GnRH	Gonadotropin Releasing Hormone
FSH	Follicle Stimulating Hormone
LH	Luteinizing Hormone
IGF	Insulin Like Growth Factor
ANS	Autonomic Nervous System
SNS	Sympathetic Nervous System
PNS	Parasympathetic Nervous System
BMI	Body Mass Index
WHR	Waist Hip Ratio
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
E/I	Expiration / Inspiration
OST	Orthostatic Standing Test
DBT	Deep Breathing Test
IHG	Isometric Hand Grip
ECG	ElectroCardioGram

HRV	Heart Rate Variability
FFT	Fast Fourier Transform
HF	High Frequency
LF	Low Frequency
VLF	Very Low Frequency
ECLIA	**E**lectro**c**hemi**l**uminescence **I**mmunoassay
MVC	Maximum Voluntary Contraction
BDI	Beck Depression Inventory
MES	2-Morpholino-ethane sulfonic acid

PLAGIARISM REPORT SCREEN SHOT



INTRODUCTION

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine & emerging lifestyle disease among reproductive age group women. This is one of the common cause for female infertility[1]. In 1935, the first systematic report of PCOS was published by Irving Stein and Michael Leventhal, the American gynaecologists, hence PCOS is also named as the Stein Leventhal syndrome[2].

According to World Health Organization (WHO) around 116 million women suffering from PCOS worldwide in 2012. Prevalence of PCOS are very inconstant, the range between 2.2% to 26%[3].Prevalence is highly variable because of using different diagnostic criteria. In India, the prevalence rate is on the rise due to the lifestyle that people have adopted. Majority of the prevalence report in our Country are hospital based, in recent times studies have done in the adolescent age group in schools, from this the prevalence of PCOS varies from 9.13% to 36% (*Nidhi R et al*)[4,5].

Aetiology & pathogenesis:

The exact pathophysiology of PCOS is complex and remains unclear. However genetic & environmental factors may play an important role in the etiopathogenesis of PCOS. Other factors like obesity, disturbance to hypothalamic-pituitary-ovarian axis may lead into PCOS[6,7]. Hyperandrogenism & Insulin resistance also contributes to the pathophysiology of PCOS. Hyperandrogenism present in 60% to 80% individuals with PCOS. Insulin resistance noticed in 50% to 80% of women with PCOS[8]. Stress plays the major role in the development of PCOS. Studies which were conducted in

mammals like monkey models & in human revealed the chronic psychosocial stress causes increased cortisol levels, insulin resistance & excessive deposition of fat in the viscera (abdominal obesity)[9,10,11,12.] Stress response is chiefly regulated through HPA axis and sympathoadrenal system[13]. Repeated or else chronic stimulation of HPA axis makes the excessive & prolonged synthesis of cortisol and catecholamine secretion[14, 15, 16]. Thus stress itself is the independent risk factor of sympathetic activation.

Clinical features of PCOS:

PCOS often comes to clinical notice due to menstrual irregularities (Anovulation or oligo-ovuluation), hyperandrogenic features like hirsutism, acne or male pattern alopecia and infertility. Hirsutism, acne, obesity and other physical features in turn lead to the **psychological distress in PCOS[17].** *Psychosocial stress increases oxidative stress[18]and indirectly contributes to the etiopathogenesis of PCOS*. Prevalence of depression and anxiety in PCOS is relatively high. This causes ***cortisol secretion abnormalities (often elevated)[19]*** in PCOS.

Apart from this, care provider have to look for the signs of insulin resistance. Central obesity & Acanthosis Nigricans is specific of Insulin resistance[20]. 50% of PCOS women are obese or overweight. Weight gain often presents first. Afterwards menstrual irregularities & hyperandrogenism features will be manifested, this shows that obesity act as a pathogenic factor in the development of PCOS.[21].

Autonomic functions in PCOS:

Autonomic nervous system governs many of the body functions through its branches, sympathetic and parasympathetic nervous system which work in a coordinated manner, sometimes acting reciprocally and sometimes synergistically to regulate visceral functions. In a healthy individual, SNS & PNS are in dynamic balance, that is called as sympathovagal balance that contributes to attain an active internal homeostasis[22,23].

Factors which contributes to PCOS are also related with increased sympathetic activity[24]. Obesity, insulin resistance, recurrent stress may lead to autonomic dysfunction which causes increased adrenergic drive and reduced vagal activity[25,26,27,28].

Diagnosis of PCOS:

Diagnosis of PCOS mainly depends on clinical presentation. It is extremely easy & practical for the easy diagnosis said by Homburg. Commonly accepted criteria to diagnose the PCOS is Rotterdam criteria[29]. Polycystic ovaries in ultrasound study is also a diagnostic feature. Laboratory evaluation of Reproductive hormones like elevated LH, Fasting glucose / insulin index < 4.5 & elevated testosterone are supportive to the diagnosis.[30]

Complications of PCOS:

PCOS in long term may lead to Cardiovascular disorders, Type 2 Diabetes Mellitus, Hypertension[31], Dyslipidemia, endothelial dysfunction, reduced vascular compliance, and atherosclerosis [32,33,34,35], 7-fold increased risk of myocardial infarction[36], metabolic Syndrome. It also may lead to infertility,

endometrial cancer, complications in Pregnancy, sleep apnoea, Non Alcoholic Steato Hepatitis[373839].

Management of PCOS:

PCOS can be treated with medical management (hormonal therapy)[40, 41], surgical approach (Laparoscopic drilling and puncture of cysts)[42] and Life style modification (in the form of Regular exercise, YOGA, Diet modification). Even though pharmacological management is beneficial in the treatment of PCOS, it has many adverse effects and requires prolonged treatment. This lead to focus of Lifestyle management as prevention and treatment modality[43].

Lifestyle including simple vegetarian wholesome diet as per the calorie requirement, regular hours of sleep (early to bed and early to rise), regular exercise or Yoga[44]. Application of Lifestyle intervention in metabolic disorder like PCOS recommended as the one of the important treatment modalities nowadays. Because it is simple to perform daily, less expensive than medical and surgical management.[45] It helps in weight reduction, improves insulin resistance and its associated features and it prevents Reproductive and metabolic problems[46]. Non pharmacological methods of treatment approach have much implications in treating the patients with stress related health problems[47].

Yoga:

Yoga is a mind body medicine, links the physical, mental and spiritual components and brings the healthy wellbeing. Regular practice of yoga enhances strength, endurance, flexibility, positive mood, empathy, self-control

etc[48]. Practice of yoga prepares the body to fight against stress by interrupting the stress pathway. From the physiological point of view, doing asana with full concentration improves body-mind coordination[49].

In earlier days, Yoga was practised by healthy people. In recent few years, emergence of various diseases related with lifestyle, stress, metabolic alteration, hormonal imbalance, emotional and functional disorders, leads to the various research on evaluation of role of YOGA as a therapeutic part on different diseases[50]. Yoga mainly encourages one step outside of the comfort area to better recognize one's self from a very different perception optimistically. Ultimately leads the better quality of life.

Role of yoga in PCOS:

Now, our divine ancient science cures PCOS without any side effects and free of cost, that is Yoga practice. YOGA is found to have positive beneficial effects on metabolic diseases and PCOS (has features very similar to the metabolic syndrome).

Yoga is a **great stress buster**. Yoga asanas will harmonize hormone production through their subtle manipulation, massaging & compressing the glands, tones and strengthens the whole reproductive system. Asanas will also force stable blood out & allows fresh blood to circulate in the internal organs. Deep relaxation brought about by asanas, keeps the adrenal and cortisol levels of stressed-out PCOS minds and bodies in check[51].

Analysis of heart rate variability (HRV) is a sensitive tool to asses sympathovagal balance or imbalance [52, 53]. Easy and simple approach to

improve the sympathovagal imbalance will be the lifestyle modification in the form of regular exercise/yoga. Hence, it is used in the present study to evaluate the effects of yoga.

Adrenal fatigue:

In 1998, Dr. James L.Wilson coined the term "**adrenal fatigue**" to find & classify a particular form of chronic tiredness that most of the individual experience. After decades of working with stressed patients, Dr. Wilson wrote an easy-to-understand guide on stress & health, **Adrenal fatigue: The 21st century stress syndrome, for the many individuals experiencing adrenal fatigue[54].**

Adrenal fatigue is the state of **functional hypoadrenia** mainly due to **stress** rather than pathological damage of the gland. Adrenal gland will be functioning but not optimally leading to inadequate production of hormones which is due to inability to manage stress appropriately[55].

When the person is exposed to stress, adrenal gland will go through the phase of alarm stage (acute reaction – increased sympathetic response, adrenaline and cortisol secretion), resistance stage (if the stress persists, body tries to cope up with stress physical, psychological and behavioural alterations will manifest in this stage and finally exhaustion phase (adrenals cannot secrete hormones in response to stress)[56, 57, 585960]. In this study, we would like to evaluate whether PCOS is associated with adrenal fatigue and also the role of yoga in improving the fatigue of adrenal gland (salivary cortisol levels).

REVIEW OF LITERATURE

Review of Literature

Polycystic ovarian syndrome

Polycystic ovarian syndrome is a common endocrine disorder which affects the woman of reproductive age group[61]. Recently PCOS is denoted as **Syndrome** '**O**' **- O**ver nourishment, **O**verproduction of Insulin, **O**varian confusion and **O**vulatory disruption[62].It's otherwise known as Stein-Leventhal Syndrome' or 'Hyperandrogenic Anovulation'[63].

Physiology of Ovulation:

During foetal development, the ovaries contain about 7 million primordial follicles. However, many undergo atresia (involution) before birth. At the time of birth, there are 2 million ova, but 50% of these are atretic. Those which are normal undergo the first part of the first meiotic division and enter a stage of arrest in prophase. Atresia continues during development, and the number of ova in both of the ovaries at the time of puberty is less than 300,000. Only one of these ova normally reaches maturity in each ovarian cycle. Just before ovulation, the first meiotic division is completed (Berne and Levy 770).

At the beginning of each cycle, several of these follicles enlarge, and a cavity forms around the ovum (antrum formation). This cavity is filled with follicular fluid. One of the follicles in one ovary grows rapidly and becomes the dominant follicle, by 6^{th} day while the others regress, forming atretic follicles. The reason for the follicle to become dominant seems to be related to the ability of the follicle to secrete the oestrogen inside which is needed for final

maturation. The primary source of circulating oestrogen is the granulosa cells of the ovaries. The cells of the theca interna of the follicle secrete androgens that are aromatized to estrogen by the granulosa cells.

At about the 14th day of the cycle, the distended follicle ruptures, and the ovum is extruded into the abdominal cavity. This is the process of ovulation

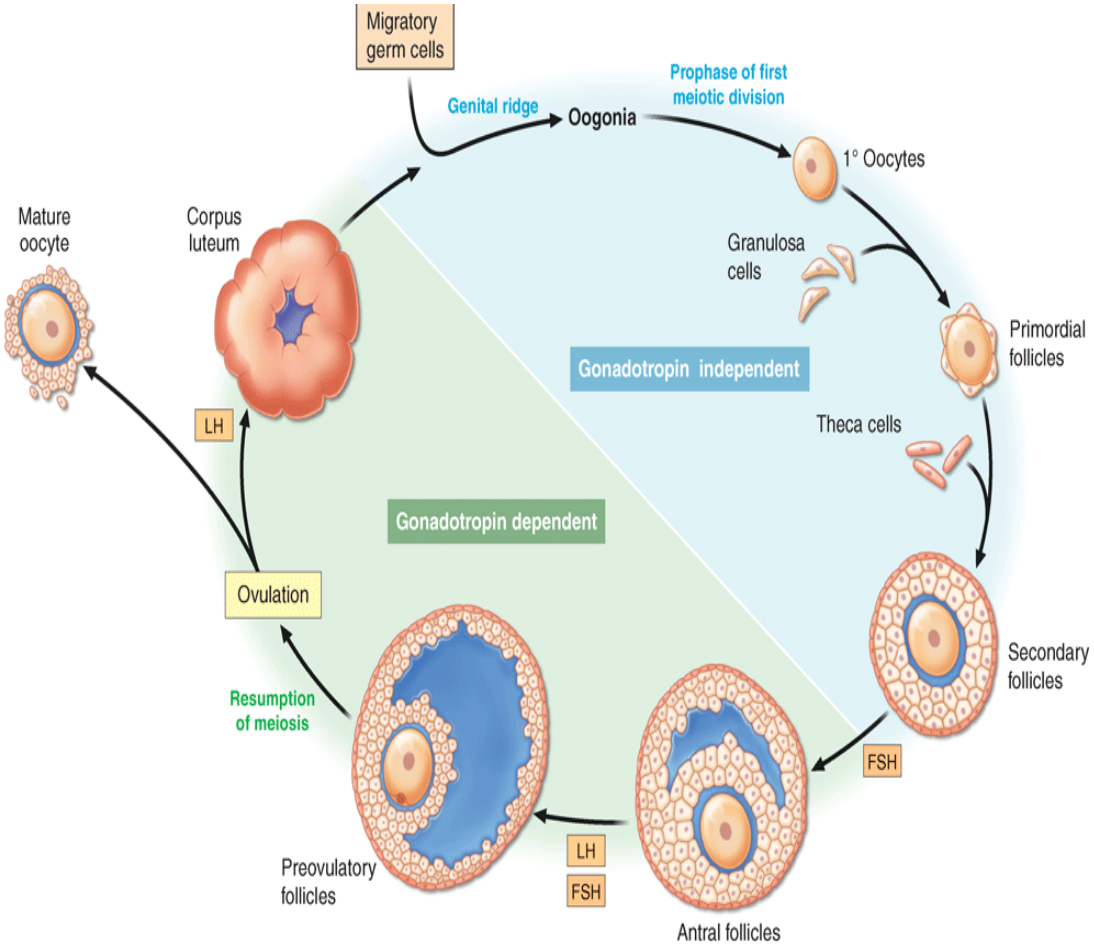


FIGURE:1 PHYSIOLOGY OF OVULATION

Hormonal changes during ovarian cycle:

FSH, LH, estradiol, and inhibin, are known as the classic hormones which transmit messages between the ovary and HPA axis. Additional factors such as IGF2, inhibin, and activin, coordinate sequential activities within the

follicle destined to ovulate. The ovarian hormones estradiol, inhibin, and progesterone suppress the secretion of FSH by a negative feedback during the early and midluteal phase. Regression of the corpus luteum causes a sudden reduction of these hormones during the late luteal phase. This favours increased secretion of FSH just before and during menstruation FSH is necessary for the recruitment of and growth of follicle and ovarian steroidogenesis. Ongoing follicular maturation requires the successful conversion from an androgenic to an estrogenic microenvironment

The rapid rise in estradiol levels triggers ovulation. A mid cycle surge of LH is produced due to a positive feedback at the anterior pituitary and the hypothalamus. This LH surge induces expulsion of the ovum and formation of the corpus luteum. Ovulation is followed by an increase in progesterone and the estradiol level causing the luteal phase. The FSH and LH levels are low in the luteal phase. The levels of progesterone, estradiol, and inhibin A falls with the disintegration of the corpus luteum. This leads to a rise in the FSH levels at the end of the luteal phase, initiating a new cycle.

Factors like activin, inhibin play a role in the follicular development and steroidogenesis. Activin produced by the granulosa cells in the early stage of follicular phase enhances the action of FSH on aromatase activity. It is necessary for the formation of FSH and LH receptor. It inhibits the formation of C19-steroid in theca cells. Inhibin is produced by the granulosa cells in the late follicular phase. Inhibin promotes the synthesis of C19 steroids in the theca layer in response to LH and local growth factors and cytokines. This provides

larger amounts of the precursor androstenedione for production of estrone and ultimately of estradiol in the granulosa cells. LH-mediated androstenedione production in theca cells and FSH-mediated estradiol production in granulosa cells are potentiated by IGFs. The major endogenous IGF produced in the human ovarian follicle is IGF2 which is produced by granulosa and theca cells. The actions of IGF1 and IGF2 are mediated by IGF receptor type1 in both cells which is structurally similar to the insulin receptor.

Ovarian steroidogenesis:

In normal menstrual phase, ovarian steroid producing cells can synthesize steroid hormones in response to FSH and LH. Steroidogenesis in ovary is same as that of Adrenal and testis. FSH receptors are most abundant and restricted to the granulosa cells. Till the late stage of follicular phase LH receptors are limited to the theca cells. After that Phase these receptors also present in granulosa cells. Theca cells that surround the follicles has rich blood supply and it takes the cholesterol from circulating Lipoprotein and synthesis of Androstenedione and Testosterone occurs. These process is under the influence of LH. Androstenedione and Testosterone enters into the granulosa cells through the basal lamina, since granulosa cells doesn't have any direct blood supply. Aromatose is the most abundant enzyme present in the granulosa cells. Under the influence of FSH, estradiol is synthesized, it is the most potent estrogen and also primary steroid of ovary during follicular phase. In luteal phase also two cell types are essential for the production of steroids which is same as that of follicular phase. Theca cells synthesize 17-

hydroxyprogesterone, a substance for aromatization to estradiol by the luteinized granulosa cells. The luteinized granulosa cells are the main source of progesterone production. LH is essential for normal function of Corpus luteum.

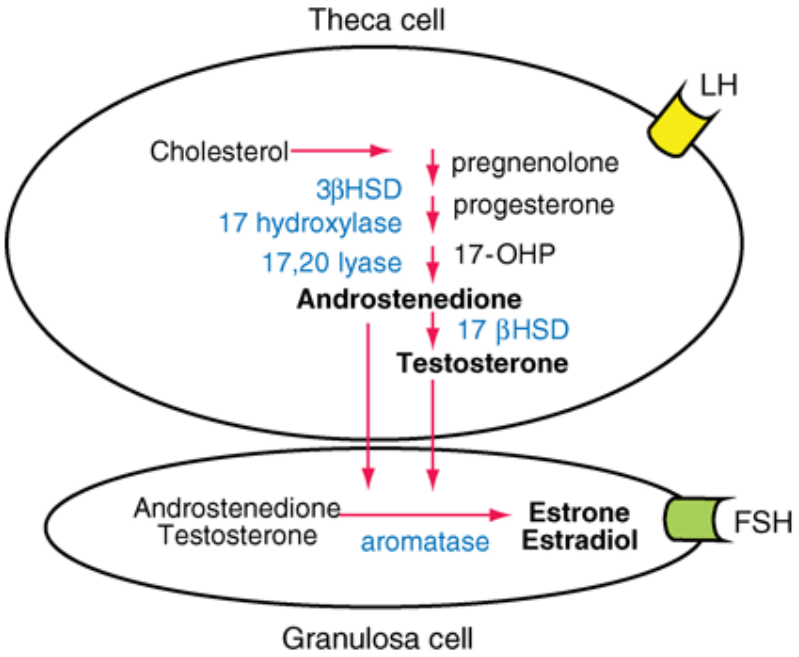


FIGURE 2: TWO CELL MODEL FOR STEROIDOGENESIS

Pregnenolone, progesterone, 17α-hydroxyprogesterone, dehydroepiandrosterone (DHEA), androstenedione, testosterone, estrone, and estradiol are secreted in the ovary. Estradiol and progesterone are biologically active whereas, androstenedione, is not biologically active. However, it is a precursor of circulating levels of estrone and testosterone in extra glandular tissues such as adipose tissue and skin. Estrogenically weak estrone is further converted to the potent estrogen, estradiol and androgenically weak testosterone is converted to the potent androgen dihydrotestosterone (DHT) locally in target tissues such as brain, breast, prostate, genital skin & subsequently exert potent biologic effects. Estradiol is produced by the

preovulatory follicle, and the corpus luteum. Progesterone is produced from the corpus luteum during the second half of the cycle under the control of LH and FSH.

Hormonal alteration in PCOS

FSH, LH (gonodotrophin) synthesis is irregular. In these women there will be an increased LH levels and decreased FSH levels were noticed. This may be due to increased sensitivity of anterior pituitary to GnRH signals. There is a greater pulsatile secretion of GnRH also detected[64]. Progesterone secretion is low or deficient in PCOS woman because of anovulatory cycles. So the negative feedback mechanism over the LH secretion is absent[65]. So these patients have high LH levels. This enhanced LH level stimulates the ovarian theca cells and increases the androgen (Androstenedione and Testosterone) production than usual. This elevated Androgens reaches the blood circulation and it endures extra ovarian aromatization, it will be converted as oestrogen in skin and adipose tissue[66 , 67]. This process says that PCOS individuals usually experiences the state of hyperandrogenism and also Hyperestrogenism. This increased estrogen levels produce an abnormal feedback mechanism on hypothalamus and anterior pituitary, this leads to reduced FSH, elevated LH levels[68]. Follicular development and maturation is affected and atresia of the follicles occurs due to low FSH & raised ovarian androgen level and that leads to anovulatory cycle[69].

LH FSH ratio may be elevated. But this ratio may not be abnormal in 10-20% of the PCOS patients[70]. GnRH pulse generator may be disturbed that leads to

abnormal LH secretion. Increased GnRH-LH pulsatile activity is the underlying cause for increased levels of LH seen in PCOS.

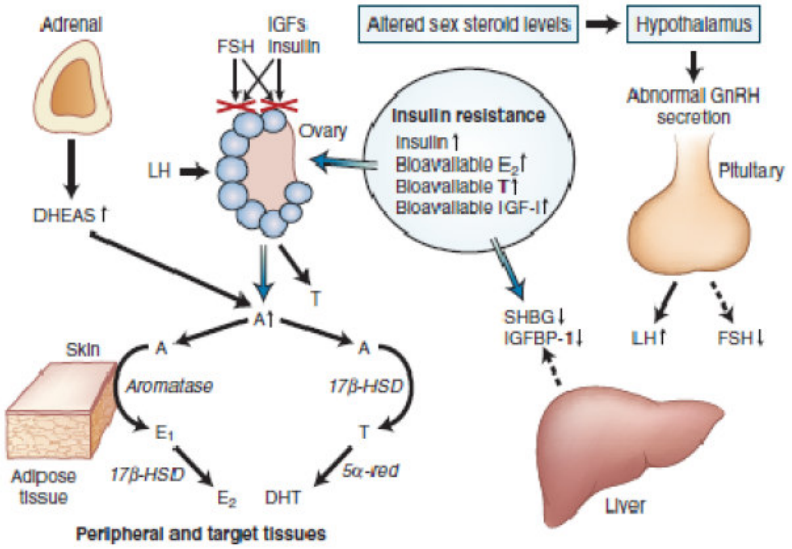


FIGURE 3: STEROID PRODUCTION IN PCOS

Aetiology & Risk factors of PCOS:

The exact direct Pathophysiology of PCOS remains not fully understood and it is unclear and complex. The etiological factor & pathophysiology is still on debate.

A. Obesity: 50% of PCOS are obese[71]
B. Insulin Resistance & Hyperinsulinemia (Insulin Resistance in skeletal muscle tissue & insulin sensitivity in adrenal and ovarian tissue[72])
C. Altered HPA axis
D. Abnormalities in ovarian (hypersecretion of androgen by ovarian theca cells[73])
E. Adrenal steroidogenesis

F. Genetic and Environmental factors[74, 75]

G. Altered activity in the sympathetic nervous system (*Greiner M,et al 2005)*

Autonomic dysfunction in PCOS:

Altered activity in the sympathetic nervous system has been suggested in aetiology of PCOS (*Greiner M,et al 2005)*[76]**.** LF-HF ratio a marker of sympathovagal balance was increased in PCOS cases, which shows the prevailing sympathetic over activity and decreased HRV (*Yildirir A, Aybar F et al.)*[77]. There are studies which have reported the decreased HRV as a significant cardiovascular risk factor[78]. *Streeter CC et al* reported stress is one of the factor that causes autonomic dysfunction[79].

Autonomic Nervous System

The term autonomic nervous system was coined by Langely in 1898 to describe that part of nervous system which controls the automatic, unconscious, involuntary functions and responsible for the motor control of the viscera.

Whenever internal stimuli signals about derangement of the internal environment, its autonomic nerves and the central nervous system (CNS) commands compensatory actions The autonomic nervous system assists the body in maintaining the constancy of internal environment (homeostasis).

Division of ANS:

The ANS is divided into Sympathetic Nervous System and Parasympathetic Nervous system and each having the central and peripheral component. The sympathetic preganglionic neurons situated in intermediolateral horn of

thoracic and upper lumbar segments (T1 to L2) of the spinal cord hence the name **thoracolumbar division**. Parasympathetic preganglionic neurons found in brainstem and intermediolateral gray horn of sacral spinal cord (S2 to S4) hence the name **craniosacral division**. Their axons leave the central nervous system and they synapse in specialized ganglia. Sympathetic postganglionic neurons are located either in paravertebral or prevertebral ganglia. Parasympathetic postganglionic neurons are located in ganglia, which lie close to or within the walls of the target organs. Postganglionic neurons (Second order neurons) innervate smooth muscle and cardiac muscle directly.

Higher centres of ANS:

Higher centres exist in brainstem, limbic system and hypothalamus. Since hypothalamus plays a vital role in the regulation of autonomic activity, it has been called the main ganglion of the ANS. (Berne and Levy, 6th edition)[80].

Neurotransmitters in ANS:

Acetylcholine is the primary neurotransmitter in both pre ganglionic and postganglionic neurons of the parasympathetic system. Nor epinephrine is the primary neurotransmitter in sympathetic end organ targets with two main subtypes of alpha and beta receptors. (Ganong, 23rd edition)[81].

Cardiovascular Autonomic Nervous System

Both sympathetic and parasympathetic nerves innervate the heart and the vascular system. ANS of the heart is under the control of cardiac autonomic centres situated in the medulla, which integrates the cardiac autonomic reflex.

Vasomotor centre is the primary cardiovascular regulatory centres located in the medulla oblongata of brainstem. The sympathetic supply is controlled by cardiac excitatory area (Pressor Area) in Rostral Ventero Lateral Medulla (RVLM). The cervical sympathetic nerves reach the heart, thus forming the efferent limb of cardiac autonomic reflexes. The parasympathetic center is located in nucleus ambiguous and dorsal motor nucleus of vagus and its output reaches the heart through the vagus nerve.

Afferent inputs from various central and peripheral organs also reach these cardiac autonomic centres. Some of the inputs excite the cardiac sympathetic centres, which in turn inhibit the parasympathetic centre. Thus there is an antagonist effect of these vital centers on each other.

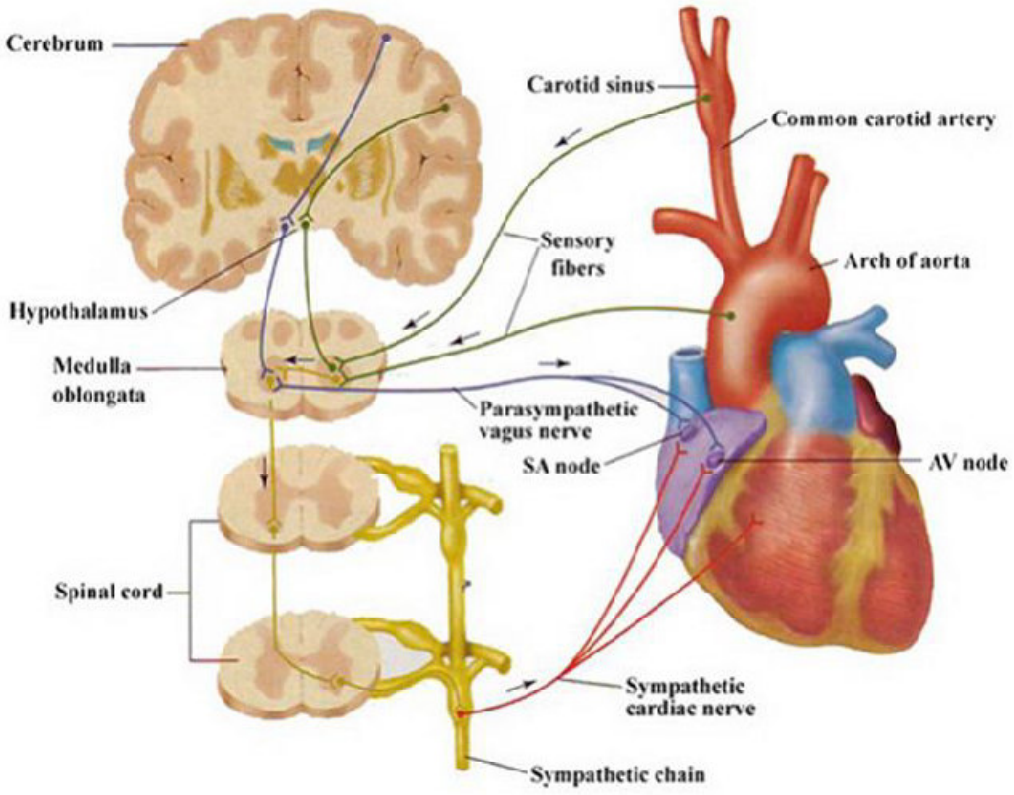


FIGURE: 4 AUTONOMIC INNERVATIONS OF THE HEART

Heart is innervated by both sympathetic and parasympathetic nerves.

Normally there exists a balance between sympathetic and parasympathetic tone and called as sympathovagal balance. In a denervated heart, where both sympathetic and parasympathetic nerves are blocked, the heart beats at the rate of 100 -110 beats/ minute which is called as the intrinsic heart rate. But the normal adult resting heart rate is around 72 beats / minute which suggest that under resting conditions the parasympathetic tone predominates.

Autonomic function testing:

The cardiovascular autonomic function tests that relies on BP, heart rate and the alterations in respect to breathing, and to postural variations are frequently used for testing the integrity of autonomic nervous system and thereby the regulation of homeostasis *(Genovelyland et al,1998)*[82]. These tests which are simple, easy to perform and reproduce, non-invasive, sensitive as well as specific are listed below:

Non-invasive tests of Autonomic Function:

Sympathetic nervous system:

1. Heart rate and BP response to active standing

2. Beat to Beat Blood pressure response to Valsalva maneuver

3 .BP and HR response during and after 5 minutes of isometric hand grip test

4. Diastolic BP and heart rate response during cold pressor test

Parasympathetic nervous system:

1. Response of heart rate (HR) to standing
2. Response of HR to deep breathing

3. Heart rate response to Valsalva maneuver

Orthostatic standing test (OST):

The heart rate during initial 30 seconds after active standing from supine position is measured. Continuous heart rate recording demonstrate that the heart rate peaks at 15th beat, starts slowing at 20th second reaching a minimum at 30th beat.

When the subject assumes the erect posture from supine position, pooling of blood towards the lower limbs occurs due to gravity causing a decreased venous return which in turn reduces the cardiac output and arterial pressure that is sensed by the arterial baroreceptors which results in baroreceptor unloading and a consequent vagal withdrawal producing an instantaneous increase in heart rate, which peaks around 15th beat after which the blood pressure returns to normal level resulting from baroreceptor mediated slowing of heart rate, which is evident around the 30th beat *(Borst et al 1982)*[83]. This test provides an estimate of the cardiac parasympathetic control as the changes in heart rate are largely mediated by parasympathetic withdrawal and activation reflecting the changes in baroreceptor afferent traffic.

Deep Breathing Test (DBT)

Heart rate variability during respiration which is known as sinus arrhythmia results from the influence of afferent vagus on the medulla by reflex feedback loops, mediated by stretch receptors located in the lungs, chest wall, heart, blood vessels and by the respiratory centers. It decreases with age and increases at slower respiratory rate at around 5-6 respiration/min. The changes

in the baroreceptor responsiveness during different phases of ventilatory cycle provide additional modulation of heart rate.

The impulses from the stretch receptors in the lungs during inspiration cause vagal inhibition and the increased venous return due to fall in intrathoracic pressure causes the stimulation of arterial stretch receptors, which produce vagal inhibition and further spill over of impulses from respiratory centre into the adjacent vagal motor neurons causes their inhibition leading to tachycardia. Conversely, expiration decreases the venous return and heart rate slows. After cooling of the vagus nerve or by atropinization it is documented that the reflex response is abolished *(Fouad et al, 1984*)[84]

Valsalva maneuver: This procedure evaluates the function of the baroreceptors. This test is done by a forced voluntary expiration of a subject against resistance. It consists of four phases. Phase I- raise in transthoracic pressure, transient elevation in BP and reduction in heart rate. Phase II- Reduced venous return resulting in low stroke volume, ultimately ends in reduced blood pressure and compensatory raise in heart rate. Phase III- End of expiration resulting in further reduced blood pressure due to pulmonary vascular expansion and heart rate increases. Phase IV–Baroreceptor activation, abrupt raise in blood pressure and bradycardia. Fall of BP at the beginning of phase II should not exceed 21 mmHg and at the end of phase II or in phase III it should return to baseline values (*Agnieszka Zygmunt et al, 2009*).

"Valsalva Ratio (VR) is derived from the longest RR interval in phase IV divided by the shortest RR interval in phase II and at the very beginning of

phase III". VR <1.21 is abnormal. VR reveals parasympathetic function, while variation in blood pressure is tells us about sympathetic activity.

Isometric Handgrip Test (IHG):

Sustained muscle contraction causes increased BP and heart rate which are due to the exercise reflex, which increases the sympathetic and reduce the parasympathetic activity. The heart rate changes by parasympathetic cholinergic function and blood pressure changes are regulated by sympathetic adrenergic function. (Textbook of Clinical neurophysiology, Misra 2nd edition)[85]

Cold Pressor Test (CPT):

Immersion of hand or foot in ice cold water causes motor reflex activation, leading to elevation in blood pressure and cardiac output, stimulated by cutaneous pain receptors. Raise in vascular resistance leads to elevation of blood pressure due to enhanced sympathetic activity (*Victor et al, 1987*)[86]

Resting Heart Rate Variability test:

Studies in last 30 years have shown a great significance between ANS and cardiac illness. (*Levy et al, 1994*)[87]

The duration of cardiac cycle of all heart beats occurring in one minute, even under resting condition is not the same. There is spontaneous beat to beat variability of RR interval in milliseconds is called as Heart rate Variability (HRV). The reason for normal fluctuation of heart rate is respiratory arrhythmia, baroreceptor reflex, circadian rhythm and thermoregulation. Research by *Hon and Lee in 1965*[88] states that, alterations in HRV preceded

before any notable changes occurred in heart rate as such in cases of foetal distress.

In 1985, *Ewing et al*[89] introduced simple test for short term study of RR difference to detect diabetic neuropathy.

Higher HRV indicates that heart more rapidly adjusts to the exterior and inner stimuli and it says that organism respond to the surroundings in healthier way. Higher HRV reflects optimal balance between SNS & PNS.

Depressed HRV indicates depressed activity of autonomic regulatory function and the ability to maintain the homeostasis. It primarily means that heart rate is monotonously regular. A low HRV, reflects the decreased capability for adjustment and possibly health injury. (*Sampler MB et al, Lele AS et al,* 1980). HRV changes might be a first sign of distress, reflecting involvement of more energy dependent sympathetic system. The decrease in biological signals variability is a warning sign of a homeokinetic self-regulation loss. HRV can reflect changes in body stress, while other physiological parameters are still in "normal" accepted ranges.

Heart rate variability (HRV) is a measure of the respiratory sinus arrhythmia. Normally the heart rate accelerates during inspiration, and decelerates during expiration. This normal phenomenon decreases with age and also under stressful conditions. Human studies on blocking the parasympathetic system using atropine (*Berntson et al, 1994*) indicate that HRV is a function of parasympathetic activity.

The resting Heart rate variability is one of the non-invasive tests to evaluate the integrity and functional state of ANS. Animal studies have shown that HRV is considered a marker of vagal activity (Brouha and Nowak, 1939).

In 2004, *Juan Sztajzel et al*, stated that "heart rate variability has emerged as a simple non-invasive method to evaluate sympathovagal balance at the sinoatrial node among the different available non-invasive techniques for assessing autonomic status".[90]

HRV analysis being highly complex, "European society of cardiology and North American society of pacing and electrophysiology" have contributed a Task Force for developing appropriate standards. The guide lines and recommendations of ***Task Force, 1996*** are followed in this study[91].

Measurement of HRV:

In this review the term HRV actually means the variability of RR intervals which is the interval between consecutive R peaks. In 1983, *Persson et al*[92] computed that the RR interval variation (RRIV), as a measure of the heart rate variability and one of the simplest and reliable test used for the evaluation of the autonomic functions of the heart.

In HRV analysis either the heart rate as a function of time or the intervals between successive QRS complexes need to be determined. Using the ECG signal it is possible to detect the regular pattern of beats using specially designed software algorithms. Such an algorithm is able to process the recording signal and determine with some precision when each beat is occurring.

Analysis of HRV:

Two broad categories of measures to standardize physiological and clinical studies were defined by the Task force, 1996.

1. Time domain methods
2. Frequency domain methods

HRV can be assessed either for a short term of 5 minutes or for a long term of 24 hours recording. Frequency domain methods should be preferred for short term recording and Time domain methods are preferred for long term recording (Task force, 1996).

Time domain methods:

Time domain measures are the simplest to calculate. By a continuous ECG record the heart rate at any given point in time and the interval between successive normal complexes is determined. Each QRS complex is detected and the so called NN interval that is all intervals between adjacent QRS complex resulting from sinus node depolarization or the instantaneous heart rate is determined. Time domain measures include the mean normal- to- normal (NN) intervals during the entire recording and statistical measures of the variance between NN intervals. In practice, RR and NN intervals usually appear to be same (Task force, 1996).

The majority of time domain metrics are statistical methods. It should be calculated over a specific and fixed period of time or epoch, either short term for 5 minutes or long term for 24 hours to carry any significance.

The SDNN is the standard deviation of these Normal to Normal intervals which are simple variable and expressed in millisecond. SDNN reflects the variability in the period of recordings. As SDNN gets reduced HRV gets reduced.

Mean HR is the Mean of the selected RR interval and Mean RR is the Mean of the selected RR series.

Frequency domain methods:

A series of normalized R-R values are processed through a mathematical operations, such as nonparametric [e.g. fast Fourier transform (FFT) based] and parametric [e.g. based on autoregressive (AR) models] methods (Marple, 1987), to analyse the frequency information contained in the recording.

The result is shown on a power spectrum, which shows a breakdown of all the frequencies (oscillations) contained in each epoch. The spectrum is calculated over the same epoch duration as the SDNN metric (long or short term) and the relative power or total power for selected sub-bands of the whole spectrum is computed.

Frequency domain Power spectral density (PSD) analysis provides the basic information of how power distributes as a function of frequency. The PSD is analysed by calculating powers and peak frequencies for different frequency bands. The three main components that are distinguished in a spectral calculation for short term ECG recording are:

High frequency power (HF, 0.15-0.4Hz): This power spectral oscillation is seen only for parasympathetic nervous system. HF power is mostly influenced by processes modulating gas exchange efficiency, respiratory sinus arrhythmia

(RSA) and activity from the Vagus nerve. This is specially blocked by parasympatholytic drugs. Even 1 minute ECG recording is enough.

Low frequency power (LF, 0.04-0.15Hz): This is an indicator for more sympathetic than parasympathetic modulation. LF frequencies show activity of the baroreflex function which maintains blood pressure and of the sympathetic system. This needs minimum of 2 minutes ECG recording.

Very low frequency power (VLF, 0-0.04Hz): The physiological explanation of the VLF component is much less defined and the existence of a specific physiological process attributable to these heart period changes might even be questioned. It is not much relevant in short term (5 minutes) ECG recordings.

Normalization of units:

LF (n.u) and HF (n.u) are the normalization of the powers which gives near 100% values of the sympathetic and parsympathetic events. They are calculated as follows:

LF (n.u) = LF power/(LF + HF power) or LF power / TP-VLF

HF (n.u) = HF power/ (LF+HF power) or HF power / TP-VLF

Total power = LF+HF power

LF/HF Ratio: This has been used as an index of global sympatho-vagal balance. Measurement of LF, HF is made in normalized units (Mallinai A et al, 1991)[93]. The distribution of LF and HF are not fixed but vary in relation to changes in the autonomic modulation of heart period.

***Aylin Yildirir M.D et al*[94]** in 2006 performed power spectral analysis of HRV to calculate the low frequency peak (LF 0.04–0.15 Hz), high-frequency peak

(HF 0.15–0.40 Hz), LF in normalized unit (LF nu), HF in normalized unit (HF nu) and LF/HF ratio in polycystic ovary syndrome (PCOS) patients and regularly cycling controls and found PCOS patients had significantly higher LF nu ($P = 0.005$) and LF/HF ratio ($P = 0.001$) and significantly lower HF ($P = 0.006$) and HF nu ($P < 0.001$) compared to controls.

Joceline cassia ferezini de sa et al in 2011 did a cross-sectional study, in which HRV and anthropometric, biochemical and hormonal parameters were measured in 23 women with PCOS and 23 age-matched controls and suggested lower SDNN, rMSSD, LF and HF indexes in PCOS women when compared to the control group. There was significant negative correlation between BMI and SDNN, LF and HF, indicating a decrease in the autonomic modulation of heart rate with increasing weight.

Kristhiane Di Domenico, M.D.,et al[95] in 2012 studied whether heart rate variability (HRV) at rest and during sympathetic stimulation is disturbed in patients with different polycystic ovary syndrome (PCOS) phenotypes in comparison to healthy controls and found mental stress promoted a significant reduction in time domain indices and HF component, and an increase in LF and LF-to-HF ratio in all groups of PCOS, indicating that it was able to induce significant vagal withdrawal and sympathetic stimulation.

Saranya et al[96] in 2013 assessed the autonomic functions in 30 age matched PCOS women and controls and found a significant increased BMI,WHR, BHR, SBP, DBP and RPP in PCOS. (LF-HF ratio), was significantly increased in cases compared to controls. Time-domain indices of HRV and E:I ratio were

decreased, and 30:15 ratio, DBP-IHG and FBG were increased in cases. PCOS patients had altered autonomic modulation in the form of increased sympathetic and decreased parasympathetic reactivity and HRV.

Göknur Tekin et al in 2007 studied heart rate recovery HRR, and the systolic BP, SBP response to exercise and heart rate variability (HRV) in patients with PCOS and have attenuated HRR and exaggerated SBP response to exercise with delayed recovery and a depressed HRV. These findings suggest alterations in autonomic neural control of the cardiovascular system in PCOS.

Insulin resistance: Studies on PCOS have clearly established that Insulin resistance or alteration in insulin secretion in an obese PCOS is more prone to develop type 2 Diabetes mellitus in their life (*Dahlgren E, Johansson S et al*.)[97]. *Legro RS, Dunaif A et al*. in their study report reveals the following:[98]

	PCOS	Non PCOS (control)
IGT (risk to develop)	31.3%	14%
DM type 2 (risk to develop)	7.5%	0%

Beta cell dysfunction is noticed in women with PCOS before the onset of glucose intolerance. Specific abnormalities of insulin metabolism identified in PCOS include reductions in secretion, reduced hepatic extraction, impaired suppression of hepatic gluconeogenesis and abnormalities in insulin receptor signalling. Insulin resistance in PCOS results in hyperinsulinaemia, associated dyslipidemia & abnormal androgen production. *(Dunaif A et al.)* [99]

Role of Stress in PCOS:

Physiologically, "*Stress* can be defined as a state in which homeostasis is jeopardized by the action of external (environmental) and internal (physiological and psychological states) stressors" (*Bozocvic, Racic, Ivkovic, 2013*). In specific to Psychological state, "stress is the experience of a perceived threat, resulting from a series of physiological responses and pathways" (*Seaward, 2012*). *Distress* defined as an interpretation that an event will have a negative and or harmful effect on the interpreter (*Ridner, 2004*), becomes increasingly problematic when the experience of stress is chronic.

Chronic stress is defined as long term repeated disruption of a homeostatic system that results in wear and tear on number of bodily functions and therefore predisposes to disease[100, 101]. Whenever a person is exposed to any kind of stress, following response will occur as shown in figure.

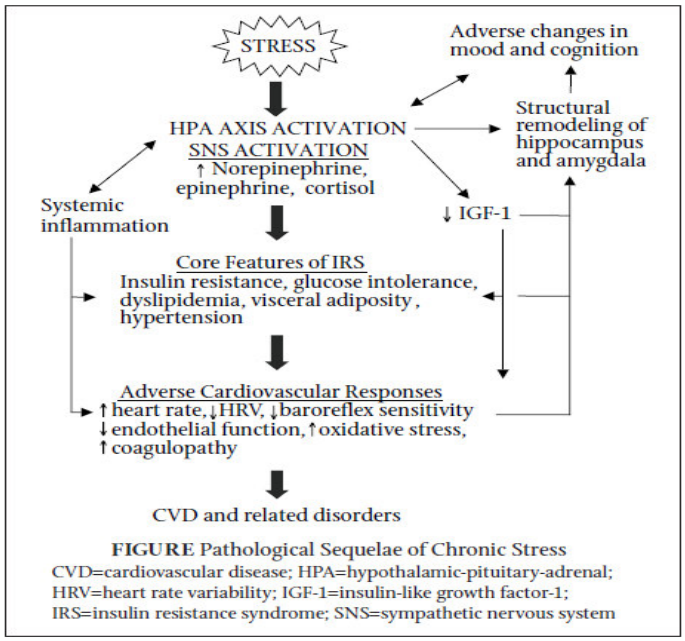


FIGURE: 5. PATHOLOGICAL SEQUELAE OF CHRONIC STRESS

The heterogeneity of PCOS may reflect multiple pathophysiologic mechanisms and the disorder itself can be initiated at any one of many entry points. **Stress** also a contributing factor in PCOS. Studies suggests that Exposure to real or perceived stress leads to alteration of Hypothalamic-pituitary-adrenal axis and sympathoadrenal system[102, 103,104]. And experiments that are done in primate models have proved that chronic psychosocial stress induces hypercortisolemia[105,106,107], insulin resistance, and visceral adiposity[108]. Chronic psychological stress also linked with increased oxidative stress[109].Thus exposure to stress plays the role in the development of PCOS by promoting the excessive activation of HPA axis, alteration in Insulin metabolism & by sympathetic overactivity.

Diamanti-Kandarakis E 2009[110] reported that **chronic stimulation of sympathetic activity, a result of stressful life style, can induce dysregulation of the Hypothalamus- Pituitary-Ovarian axis (HPO axis) in PCOS.** Association between stress and PCOS has been documented (*Trent ME, Rich M et al. 2002; Rasgon NL, Rao RC et al. 2003[111 112])*. Various research on PCOS reported that this patients have psychological features like anxiety, depression, worsened quality of life, eating disorders, social withdrawal and sickness behaviour[113]. *Barry et al.* says that patients with PCOS were significantly more neurotic (had difficulty coping with stress), anxious and depressed than the controls[114]. *Benson et al.,* reported that women with PCOS had disturbed stress responses, expressed an increased hypothalamic-pituitary-adrenal (HPA) axis and heart rate reactivity in response to a stress interview

task (2008)[115]. *L.Barnard et al*. reported that PCOS women live with Poor health-related Quality of Living and high levels of psychological distress[116].

Physical features like obesity, hirsutism, cystic acne, seborrhoea and hair loss can(most distressing features) lead to psychological distress and decrease quality of life, possibly by influencing feminine identity (*Kitzinger and Willmott, 2002)*[117].

Weiner CL. et al said that PCOS have a lower self-esteem and high negative self-image, and have high depression and **psychological distress** because of physical appearance[118].

Eggers S, Kirchengast S. et al. says that Psychosocial factors like stress may be the additional factor in the aetiology of PCOS. Its major clinical features like infertility, menstrual irregularities, hyperandrogenism and obesity could be due to high level of psychosocial stress[119, 120]. *Farrell K et al. 2000* stated that PCOS individuals, emotional distress would have psychosocial and pathophysiological causes[121]. *Pekhlivanov B, Kolarov G et al. 2006* in their study 100 adult PCOS were participated, the report was they had high negative influence on quality of living which were correlated with Hirsutism, overweight and infertility[122]. In addition, Reproductive complications like infertility and metabolic features will have a negative impact on psychology. Various study reports says the treatment of PCOS is symptom based. So there is a persistence of psychological distress and reduced quality of living even after the treatment (*Bulow et al. 2002[123]; Sonino et al.2004[124]*).Thus the treatment for PCOS should focus on both physical and Psychological aspects.

Studies reported that Women with PCOS have higher baseline cortisol than healthy individuals. Stress may be due to environmental stressor or perceived stress or due to depression accompanied with augmented release of cortisol and many neurohormonal substances that will lead to abdominal obesity and Insulin resistance[125,126].

Stressful situation may lead to the development of **depression** (*Hammen, 2005[127]; Kendler et al.1999[128]*) and **anxiet**y (*Brown et al. 1986*[129]). Stress may present with symptoms and signs of Depression, anxiety, social withdrawal, change in sleep and eating patterns, restlessness, irritability, grief, anger, memory problems[130 131].

Psychosocial stress and oxidative stress

Imbalance between production of reactive oxygen species (ROS) and antioxidant capacity may lead to oxidative stress. Oxidative stress can result either from increase in generation of ROS or any defect in functioning of antioxidant system. Studies showing oxidative stress in PCOS women have reported differing results. Presence of increased oxidative stress in both obese and lean PCOS individuals[132, 133, 134, 135, 136]. This alters and worsens the Insulin action (insulin resistance) and hyperandrogenism in PCOS[137,138]. It independently promotes endothelial dysfunction[139]. This explains why PCOS cases are more prone for cardiovascular dysfunction in their later life.

Many pathophysiological mechanism that connects psychosocial stress and PCOS by enhancing inflammation and oxidative stress.

1. There is a synthesis of inflammatory cytokines in the adipose tissue which is mediated by stress. This in turn leads to Insulin resistance.
2. Psychosocial stress produces reactive oxygen species.
3. Cortisol mediated inhibition of Nitric oxide synthase (NOS) activity, resulting stimulation of production of cytokines and reactive oxygen species[140, 141, 142]

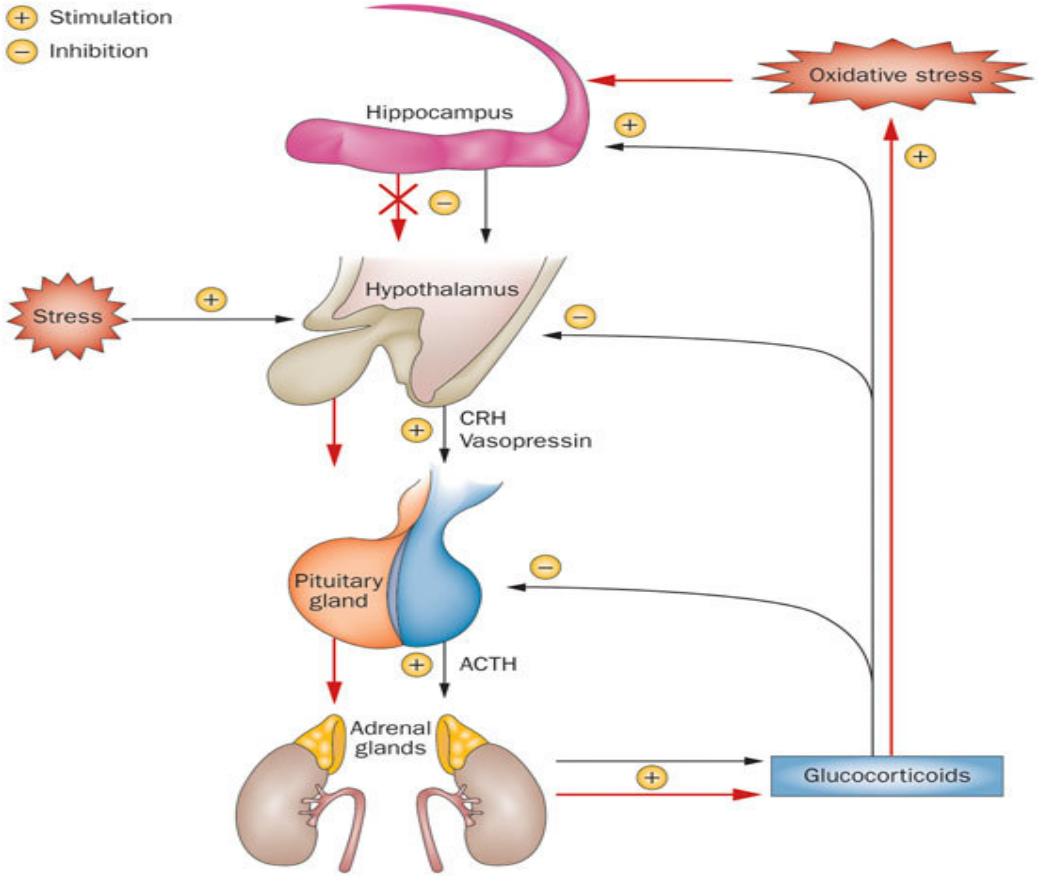


FIGURE:6. CORRELATION OF STRESS AND OXIDATIVE STRESS

Thus psychosocial stress promotes oxidative stress and indirectly plays a role in the development of PCOS.

Genetics of PCOS: The PCOS phenotype is a consequence of genes and environment. Obesity associated with unhealthy lifestyle choices aggravates

PCOS phenotype in genetically susceptible women. Several genomic loci have been proposed to account for the PCOS phenotype. These include *CYP11A1*, the insulin gene, and the follistatin gene.(*Diamanti-Kandarakis E,et al.2006*)

Clinical features:

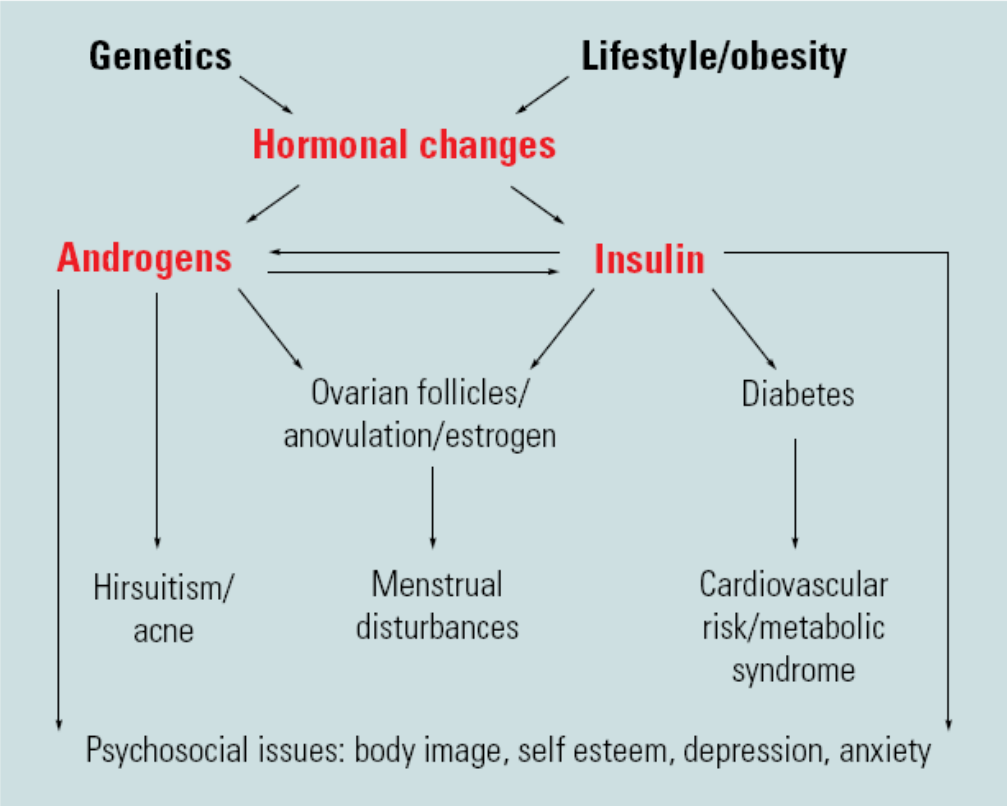


FIGURE: 7 FACTORS INFLUENCING PCOS

1. Menstrual irregularities with oligo or anovulation
2. Features of Androgen excess - hirsutism, acne & male pattern alopecia
3. Infertility , spontaneous pregnancy loss
4. Insulin resistance & its related presentation
5. Obesity
6. Psychological features like depression, anxiety, eating disorders, social withdrawal

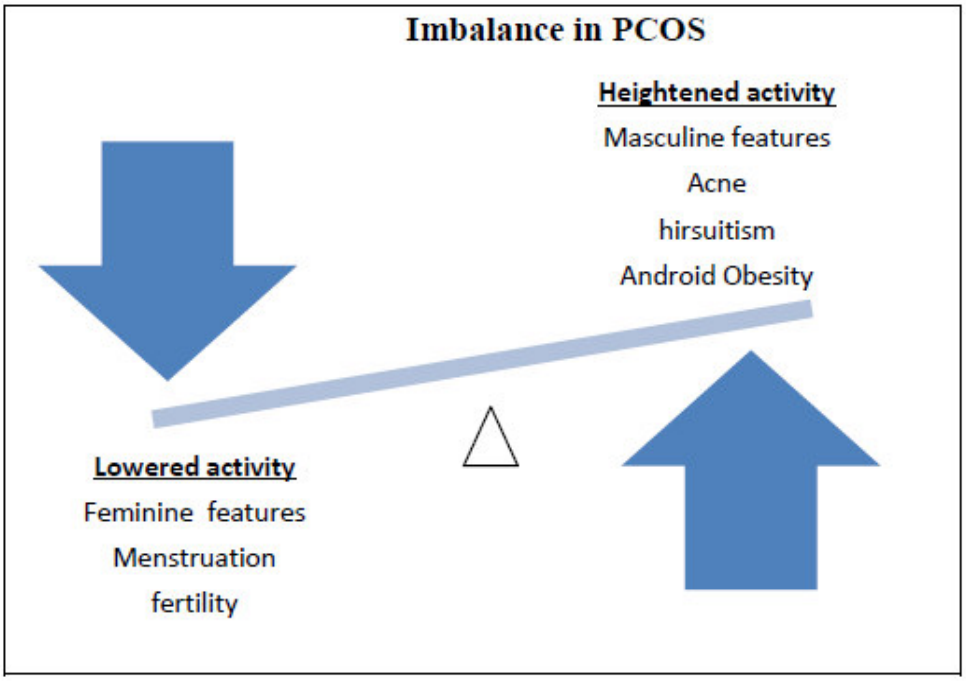


FIGURE:8 IMBALANCE IN PCOS

Menstrual irregularities:

Menstrual irregularities are more common in PCOS. Chronic anovulation presents as any the following forms; oligomenorrhea, amenorrhea and prolonged erratic bleeding. 85% - 90% of women with oligomenorrhea and 30% - 40% of women with amenorrhea have PCOS. But 30% of women with PCOS have normal menstrual cycle[143,144, 145.] In few cases irregular menstruation present since their Puberty.

Hyperandrogenism:

More than 80% of women with features of hyperandrogenism have PCOS[146].

Hirsutism: Hirsutism is the most common clinical picture of hyperandrogenism occurring in up to 70% of women with PCOS[147]. 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.). More than 90% of women with normal regular menstrual cycles with Hirsutism have polycystic ovaries. In addition, PCOS occurs in 50% of women with less severe distribution of unwanted hair growth.

Acne: It is also an indicative sign of Hyperandrogenism. Around 15%-30% of PCOS woman has acne[148,149].

Alopecia: Male pattern alopecia is the other feature of high androgen levels. Its prevalence is around 5-50%[150].

Polycystic ovaries: To diagnose polycystic ovaries there should be 12 or more follicles of 2-9 mm diameter or ovarian volume also increased (> $10cm^3$). These features in one ovary itself enough for the diagnosis of polycystic ovaries[151].

Infertility: 90 – 95% of the women who are all attending to infertility clinic with anovulatory features are diagnosed to have PCOS (*Brassard M, AinMelk Y et al.*)[152]. PCOS is the most common cause of infertility due to anovulation. Obese PCOS are poorly responsive to medical management which induces ovulation and thereby there is decreased rate of pregnancy than non-obese PCOS (*Galtier – Dereure et al.*)[153]. In PCOS women who are all infertile, 90% of them are obese. Obesity itself aggravates infertility[41].

Other Reproductive features: Miscarriage, pregnancy-induced diabetes (gestational diabetes), pregnancy-induced hypertensive disorders and neonatal complications and increased endometrial hyperplasia[154].

Depression in PCOS: Prevalence of depression in PCOS is high about 40% (*Kerchner A et al*[155]. *Rasgon et al., 2003; Trent et al*[156,157]*, 2002, 2003, 2005; Weiner et al*[158]*, 2004; Hahn et al., 2005). Benson S*[159] *2009 et al, Tan S*[160] *2008* et al, reported says that 23.9% and 25.2% of women with PCOS had mild to moderate and clinically relevant ranges of depression on the Beck Depression Inventory (BDI), respectively.

Rasgon et al. [161](2003) stated that enhanced levels of Insulin resistance and increased body mass indices (BMIs) were related with depression in PCOS individuals. *Hahn et al*[162]. (2005) said that that obesity and Hirsutism but not acne, infertility or testosterone levels are correlated to the decreased quality of living.

Studies which were conducted in animals says that chronic mild stress can produce depression and elevation of pro-inflammatory cytokines. But in human studies the results are varying (*Gold SM, Irwin MR et al.2009, Kubera M et al 1996*)[163,164]

Adali et al reported that PCOS women had significantly higher waist hip ratio and obesity, in these **patients significant increased level of emotional distress and depression** were noticed than the control population[165]. This reports are in accordance with earlier studies which says that obesity would be the threat in the development of psychosocial distress and depression in PCOS. (*Trent ME, Rich M et al., Elsenbruch S, Benson S et al., Rasgon NL, Rao RC et al)*[166,167,168].

***Hollinrake et al 2007*, Evidence of elevated cortisol levels have been reported in Depression and there would be a high sympathetic over activity** and reduced serotonin levels. This features are concomitant with Insulin resistance[169].

Parianate CM et al, 2001[170] reported that depression has increased cortisol level and increased inflammatory markers.

Depression decreases the motivation[171], this leads to the consequence on the management of PCOS. Thus treatment of depression has positive effect on the management of PCOS (*willmott 2000*)[172].

Stress reduction program improves the autonomic dysfunction, reduces the levels of anxiety and depression[173 174 175]

Anxiety:

Benson S et al. 2009 proved that PCOS women show high prevalence of anxiety about 34%[176]. *Sonino N et al 1993, Mallon E et al 1999* reported that hirsutism and acne are associated with higher level of anxiety and high psychotic symptoms in PCOS women[177,178.] Research on psychological features of PCOS revealed that anxiety is a risk element for the progression of depressive illness (*Belzer K et al.2004[179], Culpepper L. et al, 2006[180]*) and suicide attempts (*Stein MB et al, 2006[181]*) which have an increased prevalence in PCOS patients (*Mansson M, et al, 2008*[182])

Other psychological disturbances are reported in PCOS as a consequence of significant anxiety like high daytime sleep, fatigue, high difficulty in falling asleep, sleep disordered breathing(*Forbes EE et al, 2008, Vgontzas AN et al*

2001) [183,184]. *S. Elsenbruch, et al.*, reported that negative body image is the significant factor for development of depression and anxiety, decreased quality of life[185]

Other psychological features: Eating disorders, low self-esteem, sleep disturbances, negative body image, psychosexual dysfunction, reduced psychosocial wellbeing on motivation, reduced quality of life[186]

Diagnostic criteria of PCOS: [187, 188, 189]

Commonly accepted criteria to diagnose the PCOS is Rotterdam criteria[190].

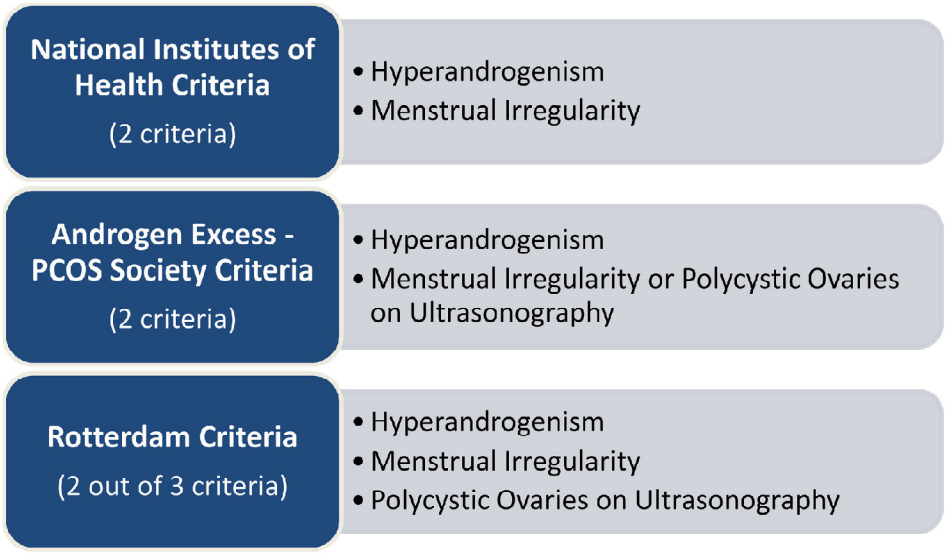


FIGURE:9 DIAGNOSTIC CRITERIA OF PCOS

Treatment for PCOS:

Medical management:

Management options focuses on three acute features; Menstrual dysfunction, Hyperandrogenism, Infertility, weight reduction. Prevention of the long-term complications related with PCOS (type 2 diabetes, dyslipidemia and cardiovascular disease).

Menstrual irregularities: Oral contraceptive pills are very useful in the management of menstrual dysfunction.it regularizes the menstrual cycle[191]. OCPs are contraindicated in women with Past history of Deep venous thrombosis or Hypercoagulability or women with above 35years with personal history of Smoking. Metformin therapy (biguanides) improves the menstrual problem, study report says that 40-90% of the individuals regained their ovulatory cycles by using metformin (*Nestler JE et al*)[192,193,194,195]. Weight reduction therapy (lifestyle modification) shows improvement in menstrual dysfunction (*kiddy et al*)[196].

Hyperandrogenism:

Hirsutism: Decreasing testosterone synthesis:

OCPs comes as the first line of management[197].

Metformin and lifestyle modification (weight reduction) decreases hyperinsulinemia and decreases testosterone levels (*Harborne L et al*.)[198]. If there is no signs of improvement with OCPs even after 6 months of treatment, Antiandrogens may be added.

Decreasing testosterone Action: Antiandrogens – Spironolactone (Aldosterone Antagonist) decreases Hirsutism by 40%[199,200]. OCPs and Antiandrogens can be used together and its response is higher about 75%[201].

Mechanical: Some patients goes for an option of laser hair removal and mechanical hair removal (plucking / shaving / electrolysis)[202].

Acne and Alopecia: OCPs and Antiandrogens are used for the management of acne and alopecia[203]. Isotretinoin may be beneficial in severe cases of acne[204].

Infertility: Clomiphene citrate is the 1st line drug for ovulation induction in PCOS woman[205]. It comes under the group of partially selective estrogen receptor modulator. Clomiphene's Ovulation rate is 75% - 80%[206].Next line of Ovulation induction includes Gonadotropins & Laparoscopic Ovarian drilling[207]. Thiazolidinediones (Tzds) and metformin are effective in the management of ovulation induction[208].

Bariatric surgery increases cycle regularity, ovulation, and chances of natural pregnancy. Various researches shown that even a weight reduction of 5%–10% improves the rate of ovulation and pregnancy[209, 210,211, 212]

Surgical management:

Laparoscopic drilling or Puncture of not more than 4 cysts in each ovary either by laser or by unipolar cautery[213].

Lifestyle modification:

Most of the PCOS individuals need the treatment for long duration. Even though medical management is effective, it has many side effects. Now there is a need of lifestyle intervention as an alternative for medical therapy. Lifestyle intervention includes Diet modification, Regular Exercise, Yoga. Lifestyle intervention reduces the metabolic features like Hyperandrogenism, insulin resistance and reduces the obesity, along with this there is an improvement in reproductive abnormalities like menstrual dysfunction, infertility and also improves the Psychological features of PCOS. It is most effective and free of adverse reactions (*Clark 1998; Huber-Buchholz 1999; Moran 2003 et al.*)[214,215, 216,]

Diet modification:

Low fat diet helps in weight reduction, thus it improves the metabolic and reproductive abnormalities in PCOS cases. Along with this high protein and low carbohydrate diet is recommended. This diet regiment aids in weight reduction and improves the insulin sensitivity (*Mikkelsen PB, Toubro S, Skov AR et al.*)[217,218].

Exercise:

Regular Exercise is preferred in the lifestyle management of PCOS. Regular exercise seems to produce enhancement in Ovulation and leads to increase in Pregnancy rate. Study on lifestyle (combination of exercise and diet) therapy leads to improvement in ovulation of 60% in PCOS cases[219]. (*Huber-Buchholz MM, Carey DGP, Norman RJ et al*.). 24 weeks of regular exercise leads to improvement in reproductive features and insulin resistance in PCOS compared to diet therapy alone (*Palomba S, Giallauria F et al*.)[220].

Yoga:

Yogic life style, a form of holistic mind-body medicine, is simple and can be practiced by all. Yoga is also easy and inexpensive to maintain, requiring little in the way of equipment or professional personnel, with some studies indicating excellent long-term adherence and benefits[221].

History of YOGA:

4000 year old tradition YOGA, nowadays becoming popular in this modern world. National institute of health classified this holistic approach ie. Yoga as complementary and alternative medicine (CAM)[222].

Yoga – derived from Sanskrit word "**YUJ**" that means joining the physical body with mind[223]. Yoga is a journey towards self-perfection with ultimate aim of achieving union with Divine[224].

Patanjali Rishi is known as the father of YOGA. He organised the "*Yoga into eight limbed path" [225, 226]*. His YOGA sutras still plays an important role in the modern yoga. In the treatment and prevention of disease patanjali's different concept has its own specific value[227].

Various schools of YOGA[228] namely: Hatha yoga (union by bodily mystery), Raja yoga (union by mental mystery), Jnana yoga (union by Knowledge), Bhakthi yoga (union by love and devotion), Karma yoga (union by action and service), Internal Yoga**.**

History of YOGA in India:

The 1st systematic therapeutic medical application of yoga started in India at Yoga Institute of Versova near Mumbai in 1918, the precursosr of Yoga institute at Santa cruz[229].

Successively yoga therapy has proliferated all over India with the establishment of Yoga hospitals & Yoga clinics. This was spread all over the World and importance of Yoga was rejuvenated. This leads to the emergence of Yoga hospital and affiliated Alternative medicine centres and establishment of Yoga therapist. Scientific evaluation of Role of Yoga on Human physiology and how yoga interrupts the pathophysiology of various diseases are appraised in recent years.

Among the various schools of Yoga, Hatha Yoga and meditation widely practiced all over the world in our modern lifestyle[230]. Hatha yoga improves the physical health by use of body postures, asanas and pranayamas (breathing techniques).

YOGA and ASANA:

Yoga is a system of physical and mental discipline. Relaxation of mind body complex. Asana means posture and consists of bodily manipulation by stretching the muscles and joints.

More than 80 asanas described in Hathayogapradipika basic booko of hatha yoga compiled by Svatmarama Yogindra in 15th century.

Asanas are classified into 3 main groups:

1. Asanas For relaxation, 2. Asanas for physical exercise 3. Asanas For meditation

In those days, yoga was practiced by healthy people. In recent years therapeutic yoga has come on action. Therapeutic yoga means application of Yoga postures and practice to the treatment of many diseases which can be organic or functional, particularly yoga treats stress related illness[231]. Studies reported that *meditation leads to decrease in cortisol and adrenaline levels*[232, 233].

Autonomic dysfunction and yoga:

Sarita Kanojia, VivekKumar Sharma et al[234] reported that regular practice of yoga has beneficial effects on both phases of menstrual cycle by bringing parasympatho dominance and psychological well-being probably by balancing neuro-endocrinal axis. *Parshad O*[235] reported that physical postures and

breathing during Yoga improves muscle strength, blood circulation and hormonal balance. It brings the autonomic system stability towards parasympathetic dominance.

In a study conducted in Diabetes individuals Yoga has shown beneficial effects as follows: decreases lipid profile, oxidative stress and blood pressure and it balances the autonomic nervous system. Apart from this yoga helps in reduction of weight, BMI, waist hip ratio and it reduces the stress, improves the psychological wellbeing[236, 237, 238, 239].

Yoga on Psychological factors like Stress, Anxiety Depression:

Andrade RL & Pedrao LJ[240] says that regular practice of Yoga improves memory, reduces emotional tension, anxiety, depression and irritability.

10 weeks hatha yoga intervention on 131 subjects with mild to moderate levels of stress, there was improvement in stress, anxiety and health status comparable to relaxation only (*Smith C, Hancock H et al. 2007 June*[241]).

Aarti Sood Mahajan et al. reported that Yoga improves the metabolic Profile. Yoga has been reported to decrease perceived stress (*Latha and Kaliappan K 1991*[242]*; Walia IJ, Mehra P et al. 1992*[243]*; Sahajpal P and Ralte R 2000*[244]) and reactivity to stressors (*Schell F, Allolio B et al. 1994*[245]), enhance stress related coping (*Nespor K 1993*[246]*; Shannahoff-Khalsa DS, Ray LE et al. 1999*[247]), reduce symptoms of depression (*Berger B and Owen D*[248] *1992; Ernst E, Rand J et al*[249]*. 1998; Janakiramaiah N, Gangadhar B et al. 2000; Mishra M* and *Sinha RK 2001*[250]*; Ray U, Mukhopadhyaya S et al. 2001; Jorm A, Christensen H et al. 2002*[251]) and anxiety (*Berger B and Owen D 1992*[252]*; Nespor K*

1993[253]*; Telles S and Naveen K 1997*[254]*; Shannahoff-Khalsa DS, Ray LE et al. 1999; Ray U, Mukhopadhyaya S et al. 2001; Woolery AMH, Sternlieb B et al. 2004*[255]*; Bijlani RL, Vempati RP et al. 2005*[256]. Yoga reduces oxidative stress but aerobic exercise increases (*Laaksonen DE, Atalay M et al. 1996; LL 1999*). Pranayama has the effect of relaxation on sympathetic nervous system, in that way reduces the stress levels (*Telles S, Nagarathna R et al. 1994*[257]). *Chatta et al* (2008) reported that 8weeks of yoga therapy decreases climacteric symptoms, perceived stress, and neuroticism in perimenopausal women better than physical exercise (*Chattha R, Nagarathna R et al. 2008*[258]) Yoga reduce stress (*Sahajpal P and Ralte R 2000*[259]) and sympathetic tone (*Manjunath NK and Telles S 2003 Jan*[260]).

Stress	Yoga-Based Practices
↑ Sympathetic Nervous System (SNS)	↑ Parasympathetic Nervous System
↑ Hypothalamic-pituitary-adrenal Axis	↓ Hypothalamic-pituitary-adrenal Axis
↓ GABA Activity	↑ GABA Activity

Effect of Yoga on PCOS:

Ram nidhi et al[261]. reported that 12weeks of Yoga program in adolescents with PCOS is significantly better than physical exercise program in reducing Anxiety, perceived stress and endocrine parameters like AMH, LH and Androgens insulin levels. Improvement in Menstrual irregularities, Hirsutism, improvement in quality of life. But non-significant change in FSH, Prolactin and body weight in PCOS.

Dr. Ruta kadam, Dr. Kirtimalini Shinde et al. reported that implementation of good lifestyle with balanced diet and Yoga, pranayama,

meditation and stress free living improves the PCOS[262]. *Schmidt T, Wijga A et al .1997* conducted a study in adult healthy obese volunteers, 3 months of regular Yoga and meditation with low fat lacto – vegetarian diet program resulted in reduction of weight around 5.7kg[263].

Mahajan et al reported in their study, after 4-days of residential integrated yoga practice program followed by 14 weeks of 1 hour daily home practice, lead to a significant loss in mean body weight from 72.26 to 70.48 kg among subjects with risk factors for coronary artery disease[264].

Benefits of Yoga in PCOS: (according to Bihar school of Yoga)[265]

1. Asanas tones up the nerves and organs of pelvis and regulates the menstruation.

2. Stimulates & balances all the systems like endocrine glands, respiratory system and Reproductive system.

3. It burns the extra deposited fat and helps in weight reduction.

4. Calms the mind and relieves the stress and other related disorders like anxiety and depression.

5. Breathing, chanting, and relaxation practices decrease autonomic imbalance leading to improved mood, decreased anxiety and improved health**.**

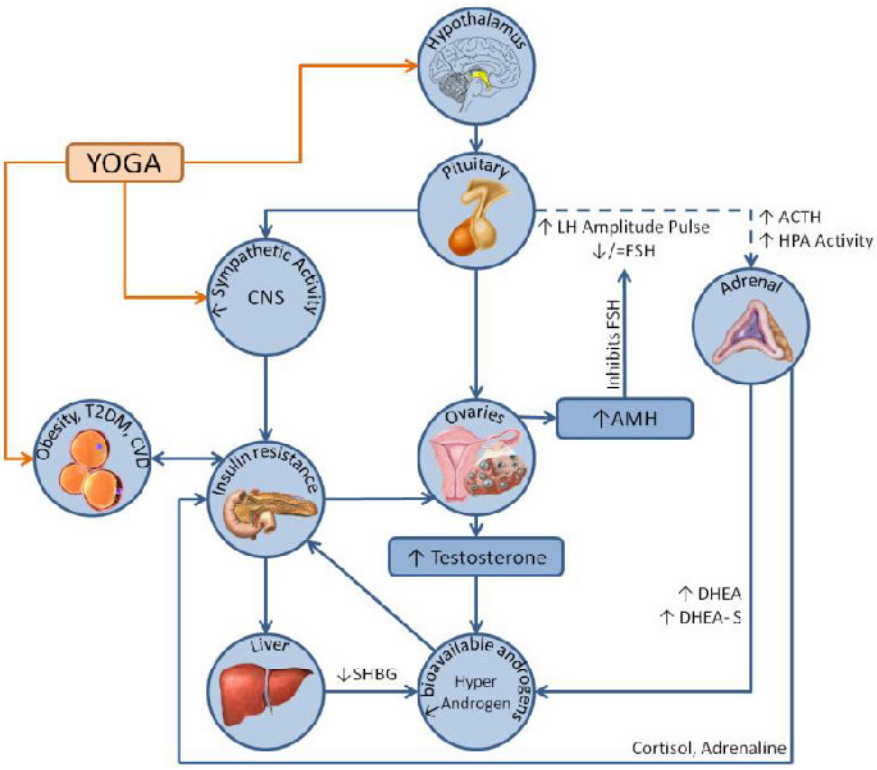


FIGURE: 10. MECHANISM OF ACTION OF YOGA ON PCOS

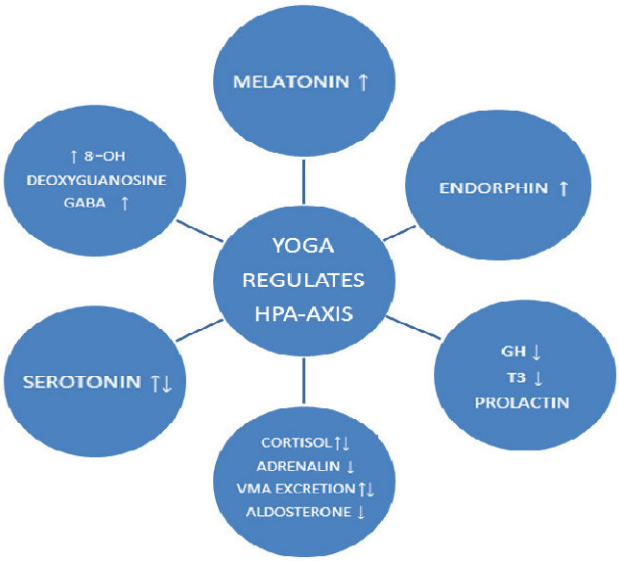


FIGURE 11. YOGA REGULATES HORMONES & NEUROTRANSMITTERS

Adrenal fatigue:

The term Adrenal fatigue or Hypoadrenia describes the maladaptive state in which Adrenal steroid production is diminished significantly due to chronic stress[266].

Extreme low end of hypoadrenia is called as Addison's disease. Other terminologies of adrenal fatigue are **non-addison's hypoadrenia, subclinical hypoadrenia, adrenal neurasthenia, adrenal apathy**[267]. Deficiency in the functioning of Adrenal glands (hypo-lower). Normally, adrenals produce little, balanced amount of steroids. Excessive Physical, psychological stress, emotional distress and environmental factors interfere in the function of adrenal and deplete its function and lowers the steroid production especially cortisol. This leads to incapability of body to perform fight or flight response. This term influenced by **Hans selye's General Adaptation system** [268, 269]

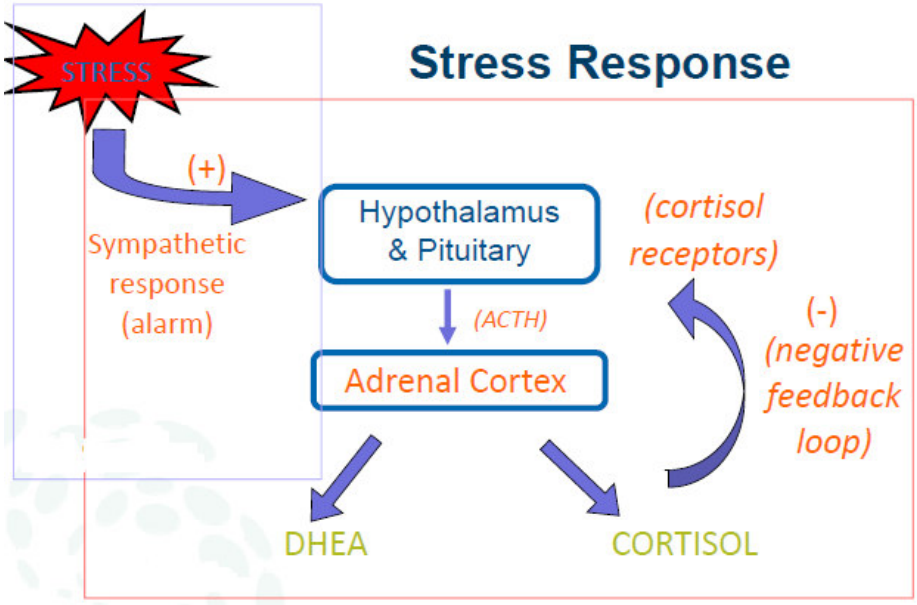


FIGURE 12: STRESS RESPONSE

Hans selye's General Adaptation System:

In 1936 Scientist Hans Selye introduced the General Adaptation syndrome model. Father of stress research**.** Prolonged physical or emotional distress can change an initial alarm phase into a stage of resistance, finally that leads to a phase of exhaustion[270].

Stages of Adrenal fatigue according to Hans selye's General Adaptation system:

ALARM REACTION:

First phase of stress reaction. This reaction occurs within 6-24 hours after exposure to stress[271]. Elevated levels of Epinephrine, Norepinephrine and Cortisol. Heart rate, blood pressure, Respiration and muscle tension increases. After this reaction there is a temporary recovery phase, that lasts 24-48 hours. During this period less cortisol will be secreted.

STAGE OF RESISTANCE:

This stage provides essential energy and circulatory changes to cope up with this stress. In this stage, the person starts feeling irritated, over reacts to minor situations and gets mentally and physically weak. Psychological, physical and behavioural changes are also clearly visible. If stimulation for stress continues, the adrenals will continue to secrete high amount of glucocorticoid. This phase can continue for years. Persistent high levels of cortisol may lead to affect the individual cells. Prolonged resistance phase increases the risk of significant disease like diabetes, high blood pressure and cancer.

STAGE OF EXHAUSTION:

During the resistance phase, there is an elevation of cortisol, along with that increase in aldosterone (mineralocorticoid) levels are present due to the stressful events. When the person enters into the exhaustion phase from the resistance phase decreased cortisol and aldosterone secretion will be manifested. This decreased cortisol and aldosterone (loss of sodium) are the reason for exhaustion phase. In this phase, if the stress still continues the person not able to manage the stress. Adrenals cannot produce the hormones because of exhaustion.

Above said phases are based on animal experiments which was established by Hans selye. He described how does animals adapt the different phases of stress.

Human response to stress:

A long phase of resistance followed by adrenal fatigue: People who fall under this type, will remain in resistance phase until their late life. They can handle the stressful events throughout their life.

A single stressor followed by adrenal fatigue: Type of adrenal fatigue occur after only one stressful event. This phase is similar to the first one except no long phase of resistance. Distinctive alarm phase followed by recovery phase but recovery is partial. Instead of progressing to resistance phase, Cortisol levels remain below average, and maintains its function at sub marginal level. This people never recover from recovery phase completely.

Repeated partial recovery followed by recurring adrenal fatigue: Common pattern when person experiences the series of stressful events. Adrenal over

functioning for a long time because of series stress, at one point the glands will go for fatigue.

They go through the repeated cycles of resistance and exhaustion after an initial alarm phase. But every time they are able to return to a stage of resistance and function with above normal levels of cortisol. These people can proceed in the stage of resistance for several years until another major stressor overcomes them, after that another long recovery phase, this lead to the stage of resistance again. Larger the stress, longer the recovery. It is possible for the full recovery if they change their lifestyle.

Gradual decline into adrenal fatigue: When people experiences many stresses over time but with every event their level of recovery diminishes. They are less able to return to high or even normal levels of cortisol. Finally their adrenals become so fatigued, they cannot handle any stressful events. Their cortisol level gradually drop to the lower levels and remain low[272].

Various test to diagnose Adrenal fatigue:

- 24 hour Urinary cortisol
- Salivary cortisol (to obtain specific information about diurnal variation)
- ACTH challenge test
- Blood test- Adrenal cortex hormones like Aldosterone, cortisol, sex hormones[273]

Cortisol – glucocorticoid released in response to stress by the activation of HPA axis. It prepares our body to respond a stressful event. Cortisol is a biomarker of stress and of HPA axis activity. Stressful events lead to stimulate

the increased levels of cortisol. Biomarker of psychosocial stress (*Selye et al., 1960; Kirschbaum et al., 1995; Eck, 1996*[274]*; Bozovic, Racic, & Ivkovic, 2013*). According to *Fries E et al., 2005* Cortisol levels very high or very low for an extensive duration, this will lead to a state of hypercortisolism or hypocortisolism respectively. This is due to the stress related events[275]. *Whitworth JA et al.2005, Nijm J et al.2009, Cohen S et al.2007, Ebrecht M et al. 2004, Hamar M et al, 2012* reported that Hypercortisolism is present in many diseases like cardiovascular diseases, type 2 Diabetes, metabolic syndrome, Depression, slow wound healing[276,277,278,279,280]. *Hinkelmann K et al.* 2013 said that Hypocortisolism[281] is due to the down regulation of HPA axis, due to the exposure of stress for a very longer duration. During the initial phase of stress there will be a hyperactive HPA axis, if the stress continues for long term, person not able to cope up with the stress exhausted stage will be obtained. HPA axis will turn into Hypoactive. Hypocortisolism is present in certain conditions like chronic fatigue syndrome, fibromyalgia, lower back pain, posttraumatic stress disorder and burnout[282,283,284,285]

Salivary cortisol:

90 – 93% cortisol bound to CBG – cortisol binding Globulin in the circulation. There may be a fluctuation in diseased conditions[286,287]. Therefore measurement of free cortisol is better than total cortisol, it is independent of CBG levels[288]. Various studies reports that salivary cortisol is considered as more sensitive[289,] than any other forms (serum, urinary) cortisol in stress research[290]. Because salivary hormone is active, unbound form, reliable,

accurate. Salivary cortisol levels are not interrupted by parotid gland salivary flow rates, food, dental care or storage conditions. Procurement of salivary samples has its own advantages like simple to collect and store the samples, stress free collection, cost effectiveness, easy transportation, applicable for large population in clinical trials[291, 292].

Salivary cortisol	Serum cortisol	Urine cortisol
More indicative of amount of hormone inside the cells, the place where hormonal reactions occur.	Indicative of hormones present outside the cells	Spill over of hormone out of the blood into urine

None of the blood or urine cortisol says about hormone present inside the cells. So salivary cortisol is the accurate indicator of free hormonal activity[293].

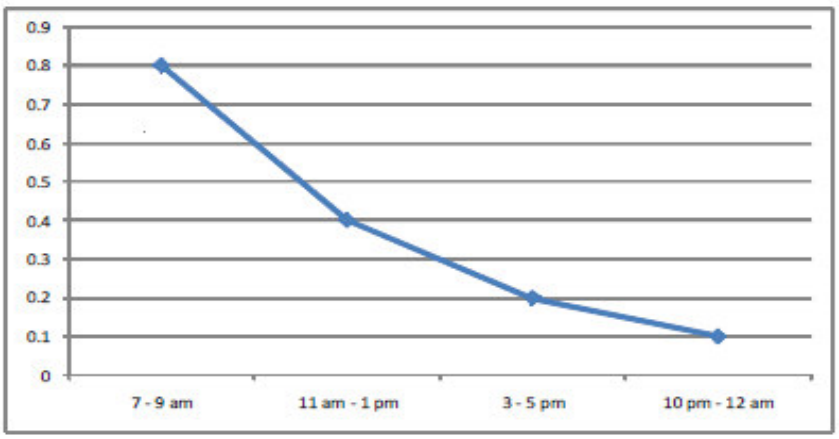


FIGURE: 13. NORMAL SALIVARY CORTISOL RELEASE PATTERN MEASURED IN MICROGRAM /DL.

Adrenal fatigue and salivary cortisol:

"*Most hormones have such a broad range of plasma levels within a normal population. As a consequence, the level of a hormone in an individual may be halved or doubled (and thus be abnormal for that person) but still be within the so-called normal range."*[294]. In adrenal function extremely low cortisol called as Addison disease and extremely high Cortisol level is called as cushing's syndrome. Other 95% represents an enormous variation in levels of adrenal function Adrenal fatigue group falls under the so called normal range of cortisol.

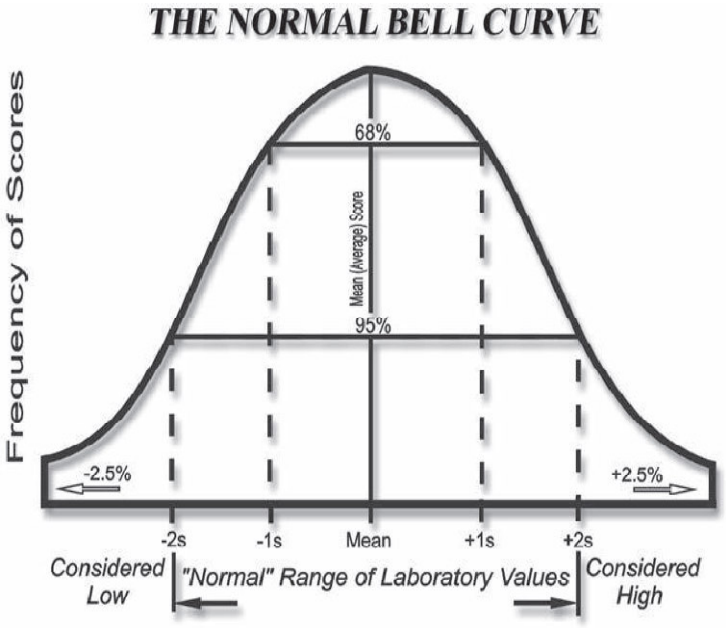


FIGURE:14 BELL CURVE SHOWING VARIATION OF CORTISOL LEVELS

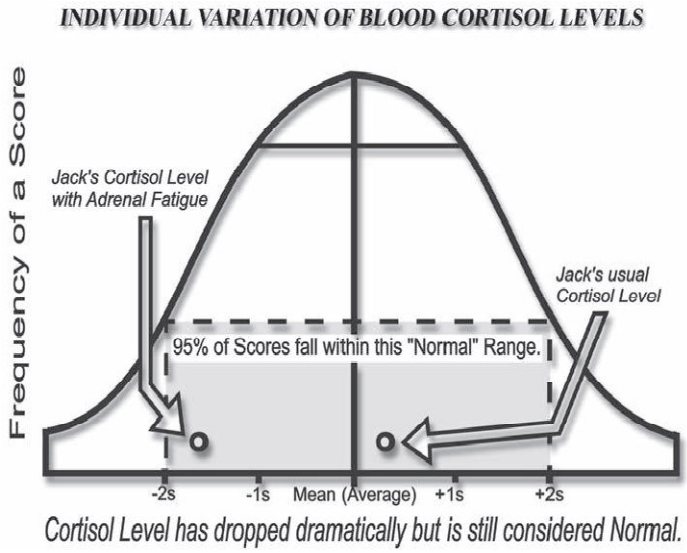


FIGURE: 15. INDIVIDUAL VARIATION OF BLOOD CORTISOL

PCOS, STRESS AND SALIVARY CORTISOL:

Tasoula tsilchorozidou et al.2003, Reported that cortisol metabolism is altered and further cortisol production is increased[295]. **Luciana Tock et al[296]** reported that *higher level of basal salivary cortisol* in PCOS individuals. **Kristen Farrell, M.S. et al**[297].reported in his review article, psychologically sound PCOS and controls were subjected to Stroop Color Word Test, which in turn produces a significant level of stress in healthy women. The Stroop test in turn triggers a significant rise in cortisol levels in PCOS than controls. During this test systolic blood pressure values were significantly higher among PCOS, this explains sympathetic nervous system activity is more harmfully affected by stress in individuals with PCOS. Cortisol is responsible for visceral adiposity and elevated inflammatory markers in response to stress. The same mechanism acts on PCOS cases.

AIM AND

OBJECTIVES

Aim and Objectives

Aim:

To evaluate the effect of yoga on Autonomic function & adrenal fatigue in Polycystic Ovarian Syndrome.

Objectives:

1. To assess and compare the changes in autonomic function in PCOS before & after 3months of Yoga.

2. To assess and compare the salivary cortisol profile (adrenal fatigue) in PCOS before and after 3months of Yoga therapy.

3. To assess and compare the psychosocial variables such as depression, anxiety, perceived stress in PCOS before and after 3months of Yoga therapy.

MATERIALS AND METHODS

Materials and Methodology

The study was conducted during the period of Sep 2015 to June 2016 at the Institute of Physiology and Experimental Medicine, Madras Medical College and Department of Yoga and Naturopathy, lifestyle and wellness clinic, Rajiv Gandhi Government General Hospital after obtaining approval from Institutional Ethics Committee (IEC), Madras Medical College, Chennai 03.

Selection of Subjects:

After obtaining informed consent, 30 females in the **age group of 18 to 30 years**, with PCOS diagnosed as per the Rotterdam's criteria, were selected from the patients attending the outpatient Department of Medical Endocrine clinic, Rajiv Gandhi Government General Hospital, Chennai - 03.

Rotterdam's criteria for PCOS (2003):

Rotterdam Criteria for Diagnosis of PCOS

Diagnosis confirmed by 2 of 3 criteria after exclusion of other etiologies:

1. Oligo and/or anovulation
2. Biomchemical and/or clinical signs of hyperandrogenism
   - Biochemical: Total T > 70 ng/dL, Androstenedione > 245ng/dL, DHEA-S >248 ug/dL)
   - Clinical: Acne, Hirsutism, acanthosis nigrans
3. Polycystic Ovaries:
   - ≥ 12 follicles (2-9mm diameter) in each ovary or ovarian volume > 10cc

FIGURE:16. ROTTERDAM CRITERIA FOR THE DIAGNOSIS OF PCOS

Based on this, the inclusion criteria for patients were defined.

Inclusion Criteria:

1. Those who satisfied the **Rotterdam Criteria for PCOS.**

2. Newly diagnosed cases and Women with PCOS but not on any treatment.

3. Women aged 18-30 years with no previous experience of Yoga or exercise.

4. No previous history of Psychiatric disorders like anxiety and depression

5. Those who satisfied the **Cohen-perceived stress scoring.**

Cohen- perceived stress scoring scale

Each item is rated on a 5-point scale ranging from never (0) to almost always (4). Scores around 13 are considered average. High stress groups usually have a stress score of around 20 points. Scores of 20 or higher are considered high stress

	Never	Almost Never	Sometimes	Fairly Often	Very Often
B.1. In the past month, how often have you been upset because of something that happened unexpectedly?	0	1	2	3	4
B.2. In the past month, how often have you felt unable to control the important things in your life?	0	1	2	3	4
B.3. In the past month, how often have you felt nervous or stressed?	0	1	2	3	4
B.4. In the past month, how often have you felt confident about your ability to handle personal problems?	0	1	2	3	4
B.5. In the past month, how often have you felt that things were going your way?	0	1	2	3	4
B.6. In the past month, how often have you found that you could not cope with all the things you had to do?	0	1	2	3	4
B.7. In the past month, how often have you been able to control irritations in your life?	0	1	2	3	4
B.8. In the past month, how often have you felt that you were on top of things?	0	1	2	3	4
B.9. In the past month, how often have you been angry because of things that happened that were outside of your control?	0	1	2	3	4
B.10. In the past month, how often have you felt that difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

Figure 17. Perceived Stress Scoring scale

	Not At All	Mildly but it didn't bother me much.	Moderately - it wasn't pleasant at times	Severely – it bothered me a lot
Numbness or tingling	0	1	2	3
Feeling hot	0	1	2	3
Wobbliness in legs	0	1	2	3
Unable to relax	0	1	2	3
Fear of worst happening	0	1	2	3
Dizzy or lightheaded	0	1	2	3
Heart pounding/racing	0	1	2	3
Unsteady	0	1	2	3
Terrified or afraid	0	1	2	3
Nervous	0	1	2	3
Feeling of choking	0	1	2	3
Hands trembling	0	1	2	3
Shaky / unsteady	0	1	2	3
Fear of losing control	0	1	2	3
Difficulty in breathing	0	1	2	3
Fear of dying	0	1	2	3
Scared	0	1	2	3
Indigestion	0	1	2	3
Faint / lightheaded	0	1	2	3
Face flushed	0	1	2	3
Hot/cold sweats	0	1	2	3
Column Sum				

Scoring **-** Sum each column. Then sum the column totals to achieve a grand score. Write that score here _____ .

FIGURE: 18. BECKS ANXIETY SCALE

Score of 0-21 indicates very low anxiety – good thing.

Score of 22-35 indicates moderate Anxiety

More than 36 indicates severe Anxiety, potential cause for concern, referred for Psychiatry evaluation.

Beck Depression Inventory

Each questionnaire consists of 21 items. The person should read each group of statements, then pick out the one statement in each group. The selection of choice of statement depend on how would the person feeling for past two

weeks including today. Don't choose more than one item in each group. Scoring based on summing the ratings for the 21 items. Each item is rated on a 4-point scale ranging from 0 to 3. The maximum total score is 63.

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

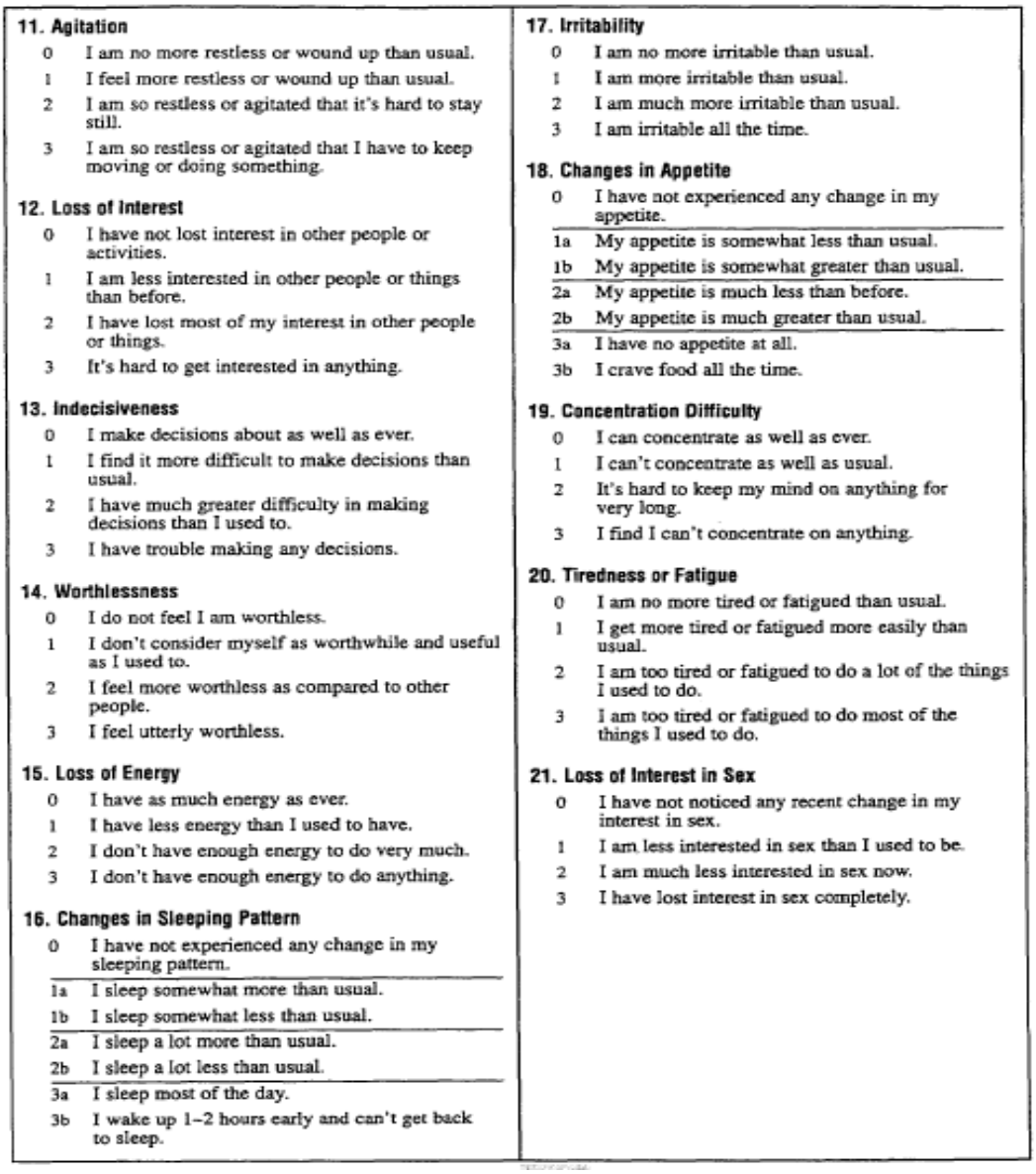
0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.



11. Agitation

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.
1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.
2a I sleep a lot more than usual.
2b I sleep a lot less than usual.
3a I sleep most of the day.
3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.
1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.
2a My appetite is much less than before.
2b My appetite is much greater than usual.
3a I have no appetite at all.
3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

FIGURE:19 BECK DEPRESSION SCALE

Score of 1- 10 – normal, 11-16 – mild mood disturbance, 17-20 - borderline clinical depression, 21-30 – moderate depression, 31-40 – severe depression, >40 extreme depression.

If score is 30 or less than 30, patient may continue the study, if the score of more than 31 should need psychiatric intervention.

Exclusion criteria:

1. Pregnancy

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

3. Conditions that mimic PCOS like ovarian hyperthecosis, hypothyroid, congenital adrenal hyperplasia and idiopathic Hirsutism

4. Subjects with neoplastic, hepatic, respiratory and any cardiovascular disorder or other medical illness.

Study design:

Interventional study

Materials required:

Physiopac Medicaid 8 channel HRV recorder

Mercury and aneroid Sphygmomanometers.

Hand grip dynamometer

Methodology:

30 women fulfilling these criteria were selected and assigned as the study group. Informed consent was obtained from all the participants.

Following which the study was initiated a thorough history was collected from all the participants including personal details such as name, age, address and phone number, medical history of any menstrual irregularities (Amenorrhoea/

Oligmenorrhoea / menorrhagia), Hyperandrogenism features like (Hirsutism, Acne, Alopecia), history of other exclusion features were collected in detail.

Physical examination:

General examination was done

Height in meters and weight in kilograms were measured and **Body Mass Index (BMI)** was calculated as **weight/height in meter square**. Their WC and HC were measured and their WHR was calculated.

WHR = Waist circumference/ Hip circumference

Height weight, waist and hip circumference were measured.

Resting blood pressure were recorded. Patients were asked to fill the following questionnaire:

1. Cohen perceived stress scoring
2. Becks Anxiety scale
3. Becks Depression scale

Thirty Subjects were subjected to a battery of autonomic function tests along with resting heart rate variability These tests examine the variability of heart rate at rest and its response to normal physiologic stimuli by various manoeuvres.

Many endogenous and environmental factors can confound the autonomic testing and need to be controlled. The following precautions were taken while performing the autonomic function tests.

1. The subjects should be relaxed, comfortable and free from recent acute illness, and without significant anxiety.

2. The autonomic function tests were carried out between 10-12 Am, 2hours after breakfast
3. Subjects were asked to remove compressive garments. Caffeine, nicotine and alcohol should be avoided 2 hours before testing.
4. The subjects were asked to empty the bladder before the test.
5. The test was performed in a quiet room with controlled temperature ranging from 25-28 degree Celsius, lighting subdued.
6. Mobile phones were switched off.
7. The subjects were instructed about various manoeuvres that would be employed and allowed to practice these manoeuvres.
8. The subjects were made to rest quietly, without moving, in the awake and supine position for a minimum period of ten minutes.
9. Electrodes were placed in the following position after cleaning the site with sprit.

HRV recording and Analysis

After 15 minutes of rest, subjects were subjected to HRV test in physiology research lab. The ECG electrodes were placed on the limbs of the subject and were connected to the leads of the machine for lead II ECG recording. The short-term 8 minutes HRV recording was performed in supine position, in morning time (room temperature maintained at 20-25 degree Celsius) using the instrument **8 Channel Physiopac of Medicaid Company**, chandigarh. The data analysis was then done using the HRV analysis software.

The spectral indices of HRV:Frequency domain measures were analysed**.**

1. PHYSIOPAC CHANNEL SYSTEM FOR RECORDING OF HRV

2. RECORDING OF RESTING HEART RATE VARIABILITY

Autonomic function tests:

Deep Breathing:

The subject was made to sit comfortably and was asked to breathe deeply and slowly as per the verbal commands such that the subject inspires deeply for a period of 5 seconds and expires slowly for 5 seconds. Thus one cycle of inspiration and expiration lasts for 10 seconds. The subject was asked to perform six such cycles lasting for about 1 minute. The average of the longest RR interval during expiration and shortest R-R interval during inspiration for 6 cycles was obtained and from this the Inspiration/Expiration ratio was calculated.

E/I ratio = longest R-R interval during expiration / Shortest R-R interval during inspiration

Isometric Handgrip Test:

Blood pressure was recorded in supine and relaxed position. The subject was asked to perform a simple exercise using hand grip dynamometer. The maximum voluntary contraction (MVC) for each was calculated by asking them to press the hand grip dynamometer with maximum force for few seconds and the same was repeated. The highest reading was taken as maximum voluntary contraction.

The subject was asked to maintain 30% of MVC as long as possible for a maximum duration of 5 minutes. Blood pressure was measured in the opposite limb during the procedure and after the procedure.

3. ORTHOSTATIC STANDING TEST

4. ISOMETRIC HANDGRIP TEST

Increase in diastolic blood pressure = Diastolic blood pressure after the procedure – Diastolic blood pressure at rest.

Orthostatic Standing Test:

After a minimum of ten minutes rest in supine position, the subject was allowed to stand immediately within few seconds for a period of five minutes, without any support and by putting equal weight on both the legs.

Blood pressure and pulse rate was recorded after 1 minute, and 3 minutes. The R-R interval at the15th beat and 30th beat was calculated.

The maximum R-R interval at 30th beat and minimum R-R interval during 15th beat gives the 30/15 ratio.

The change in systolic blood pressure after 1 minute of standing and change in diastolic blood pressure after 1 minute of standing was recorded.

30/15 ratio = Duration of longest R-R interval around 30th beat

---

Duration of shortest R-R interval around 15th beat

Collection of Salivary Samples for the estimation of Cortisol:

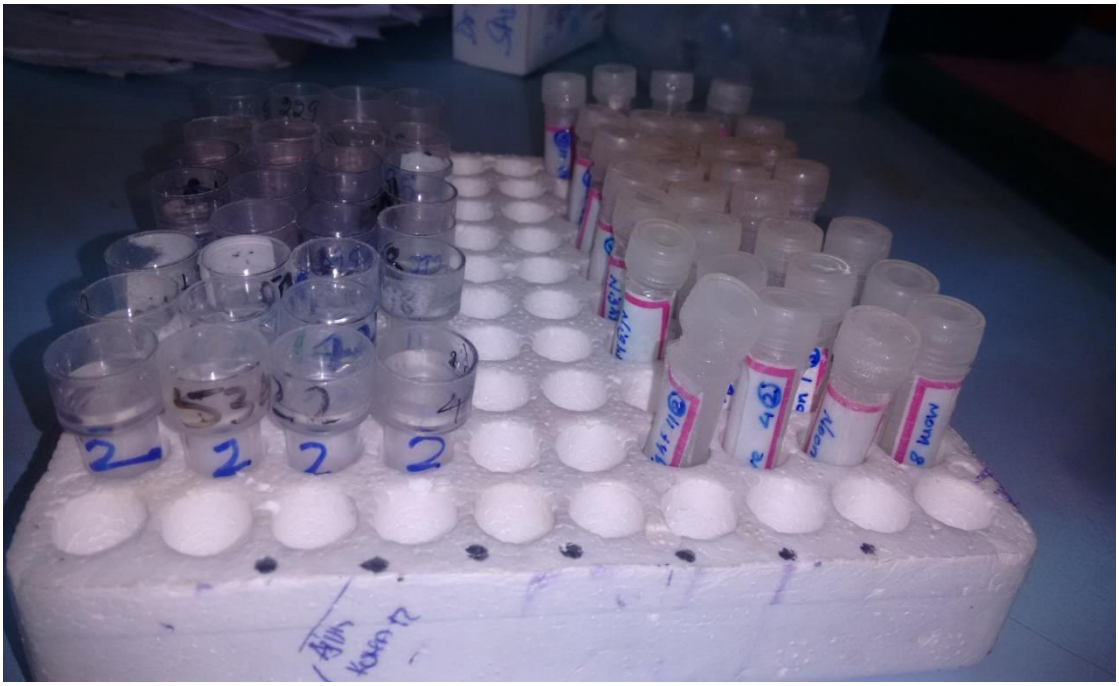
The participants are given instructions about collection of saliva in sterile tube along with sterile cotton swabs. The collection of samples were performed at four times on precise time.

1st sample – morning around 8am, 2nd sample – noon 1-2pm, 3rd sample – evening 5-6pm, 4th sample – 11.30pm-12am.

After the collection of saliva, cotton swabs were disposed safely and the samples were centrifuged (2minutes at 1000g), after that samples were stored

5. SALIVARY SAMPLE COLLECTION KIT

6. FEW SALIVARY SAMPLES



7. HUMAN SALIVARY CORTISOL KIT

8. COBAS – ECLIA READER

in a deep freezer(available at Institute of Physiology and Experimental Medicine, Madras Medical College, Chennai.) with -20 degree c temperature until estimating salivary cortisol levels.

Intervention with Yoga schedule:

The following yoga asana schedule was designed after consultation with yoga specialists and this was a perfect combination of Om chant, asanas and breathing exercises. All the patients were trained in order to the follow this yoga schedule for 90days. Patients were subjected to Yoga therapy for 45min – 1hour/day with a break of 1day after every 6days. During the study period, the participants were motivated about the importance of healthy balanced low fat diet.

(Bihar school of Yoga method were followed)

Recommended Asanas for PCOS:

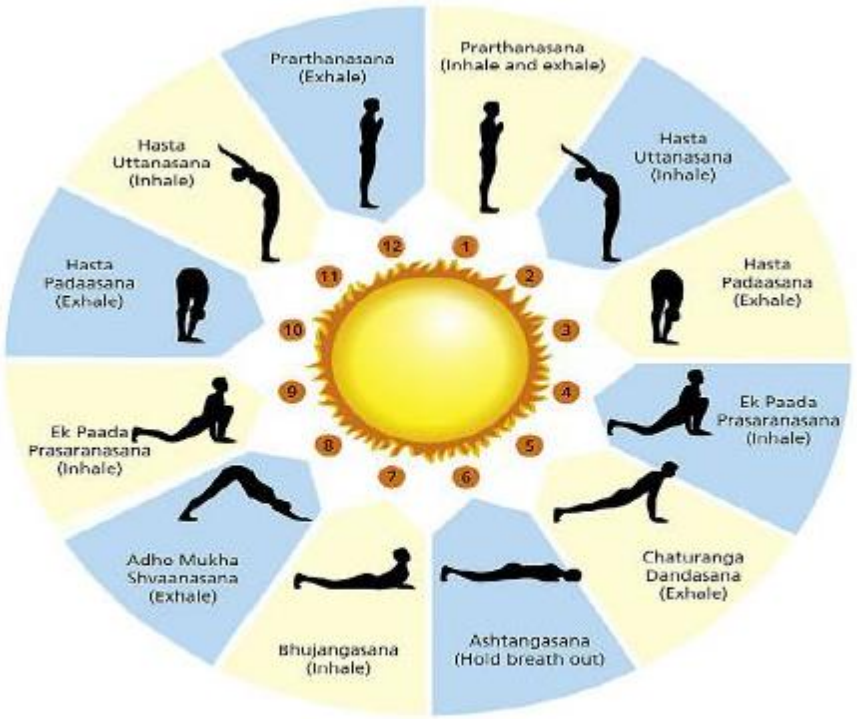
S.No	YOGA ASANA	Duration
1.	Om chanting prayer	3-5 mins
1	Surya Namaskar (6rounds)	12-15mins
2	Sakthibandasana series	8-10 min
3	Titaliasana	1 min
4	Baddhakonasana	1 min
5	Paschimotanasana	1 min
6	Shasankasana	1min
7	Vakrasana	1min
8	Bhujangasana	1 min
9	Shalabasana	1 min
10	Pranayama Nadishodhana, sheetkari & Ujjayi Pranayama	8-10m
11	Hrudaya mudra Savasana	10min
	Total	48-57min

9. FEW PARTICIPANTS PERFORMING BHUJANGASANA

10. FEW PARTICIPANTS PERFORMING PRANAYAMA

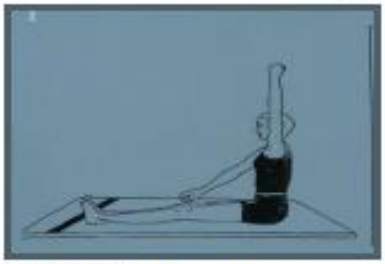
11. FEW PARTICIPANTS PERFORMING SAVASANA

YOGA ASANAS SPECIFIC FOR PCOS



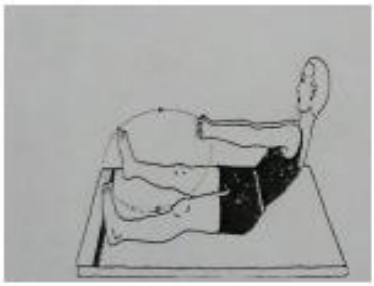
SURYA NAMASKAR

A. Sakthibandasana



1. Rajju Karshasana –
(Pulling the rope)

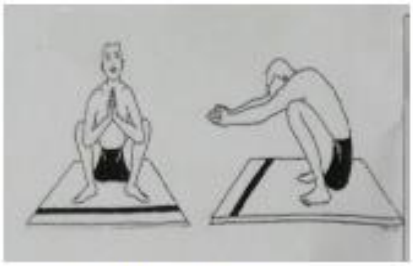
2. Gatyamak Meru Vakrasana –
(Dynamic spinal twist)



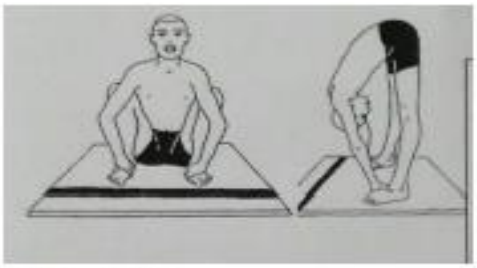
3. Chakki Chalasana –
(Churning the Mill)

4. Nauka Sanchalasana -
(Rowing the Boat)

5. Kastathakshasana –
(Chopping the Wood)



6. Namaskarasana -
(Salutation pose)



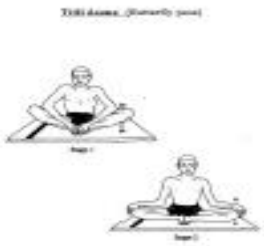
7. Vayu Nishkasana –

Wind releasing pose

8. Kauva Chalasana –

Crow walking

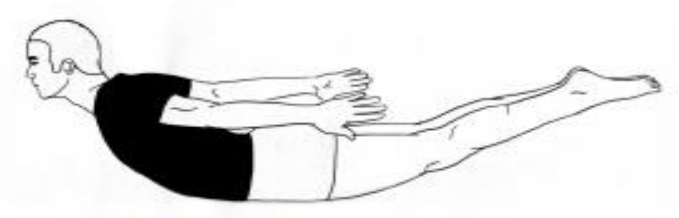
9. Udharakarshsana –
Abdominal stretch pose



B. Titaliasana -
(Butterfly pose)

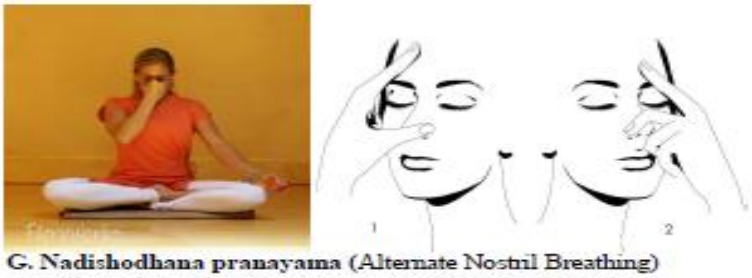
C. Baddhakonasana –
[Bound angle pose]

D. Bhujangasana -
(Cobra pose)

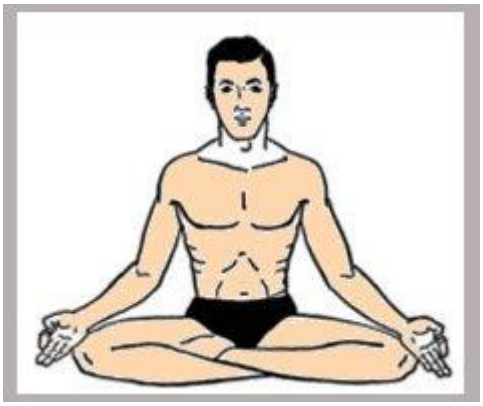


E. Shalabasana (Locust pose)

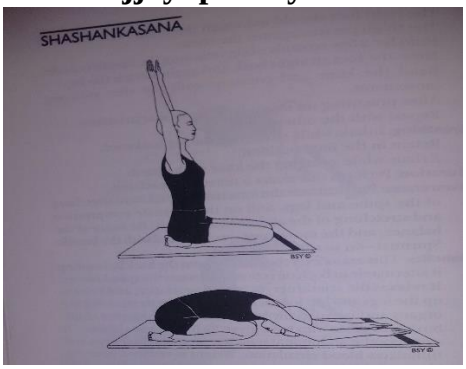
F. Paschimottanasana (two legged forward bend)



G. Nadishodhana pranayama (Alternate Nostril Breathing)



Ujjayi pranayama



SHASANKASANA

L. Savasana (Corpse pose)

M. Hrudya mudra

Estimation of Salivary cortisol:

The samples were transported in ice to the Institute of Biochemistry, RGGGH, Madras Medical College and analysed as follows:

Estimation of Salivary cortisol by ECLIA[298,299] :

Electro**c**hemi**l**uminescence **I**mmunoassay is indented for use on Cobas e immunoassay analyzers. **Kit – Cortisol II Elecsys and Cobas e analyzers Ref: O6687733190.**

Reagents – working Solutions: (pack labelled as CORT II)

M – Streptavidin-coated micro particles (transparent cap), 1 bottle, 6.5ml

Streptavidin-coated micro particles 0.72 mg/ml; preservative

R1 – Anti-cortisol-Ab-biotin (gray cap), 1bottle, 10ml

Biotinylated monoclonal anti-cortisol antibody (ovine) 20ng/ml;

Danazol 20ug /ml; MES) buffer 100mmol /l, pH 6.0; preservative

R2 – cortisol peptide – $Ru(bpy)_3^{2+}$ (black cap), 1bottle, 10ml, cortisol derivative (synthetic), labelled with ruthenium complex 20ng/ml; danazol 20ug/ml; MES buffer 100mmol /l, pH 6.0; preservative

Test Principle: ECLIA – **competitive binding assay principle**

Total duration of assay – 18minutes

Elecsys cortisol II assay makes use of a competition test principle using a monoclonal antibody which is specifically directed against cortisol. Endogenous cortisol in the sample which has been liberated from binding proteins with danazol competes with exogenous cortisol derivative in the test

which has been labeled with ruthenium complex for the binding sites on the biotinylated antibody.

1st incubation:

10ul of sample is incubated with a cortisol specific biotinylated antibody and a ruthenium complex labeled cortisol derivative. Depending on the concentration of the analyte in the sample and the formation of the respective immune complex, the labeled antibody binding is occupied in part with sample analyte and in part with ruthenylated hapten.

2nd incubation:

After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.

The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with the procell/procell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.

Results are determined via a calibration curve which is instrument specifically generated by 2point calibration & a master curve provided via reagent barcode. Values are expressed in nmol/L.

After the duration of 3months of Yoga therapy, the subjects again underwent Autonomic function test, assessment of Body Mass Index and Waist Hip Ratio, Cohen perceived stress scale, Becks Depression scale and Becks Anxiety scale

Salivary samples (4times as done in before Yoga) were collected to estimate salivary cortisol levels.

Reference normal range of salivary cortisol in ECLIA method[299]:

Morning 6-10am - <21.6nmol/L

Afternoon - 1- 2 pm - <11.03nmol/ L

Evening – 4-8 pm - <6.70nmol/ L

Midnight ± 30minutes - <5.74 nmol/L

STATISTICAL ANALYSIS

Statistical analysis was done using the software SPSS version 21.

Paired Student's t test was carried out to compare the means of variables before and after administration of Yoga therapy.

RESULTS

RESULTS

Data obtained from conducting the Autonomic Function Tests and Salivary cortisol levels, Psychological parameter scales were statistically analysed. Mean and standard deviation of the variables were determined for the cases before and after Yoga therapy. Paired T test was employed for statistical analysis as the test of significance at 95% confidence interval.

*** P value < 0.05 was considered as significant**

**** P value < 0.01 was considered as highly significant**

*****P value < 0.001 was considered as very highly significant**

RESULT TABLES:

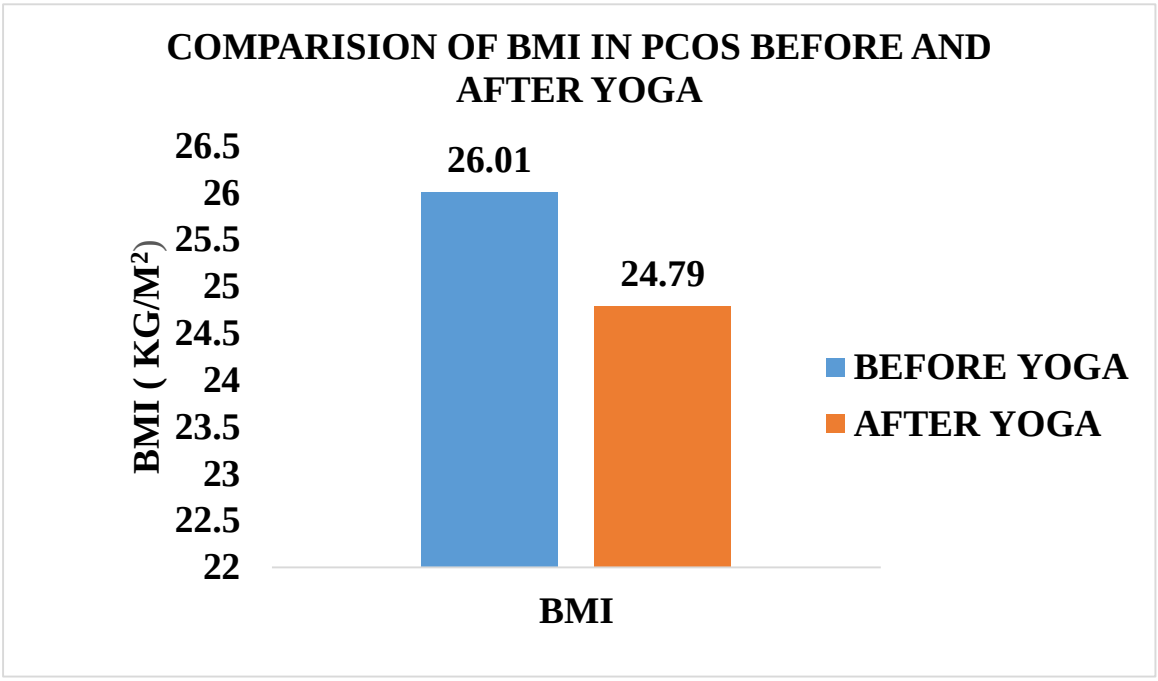
The mean age of the individuals included in the present study was 22.73 ± 1.96 years.

TABLE NO:1

COMPARISON OF BMI BEFORE AND AFTER YOGA

VARIABLE	STUDY GROUP	N	MEAN	SD	P-VALUE
BMI	BEFORE YOGA	30	26.01	3.89	
	AFTER YOGA	30	24.79	3.12	**< 0.001*** **

The mean values of BMI was found to be significantly reduced (p **< 0.001)** in the study group following Yoga therapy.


COMPARISION OF BMI IN PCOS BEFORE AND AFTER YOGA
26.5
26
25.5
25
24.5
24
23.5
23
22.5
22
BMI (KG/M2)
26.01
24.79
BEFORE YOGA
AFTER YOGA
BMI

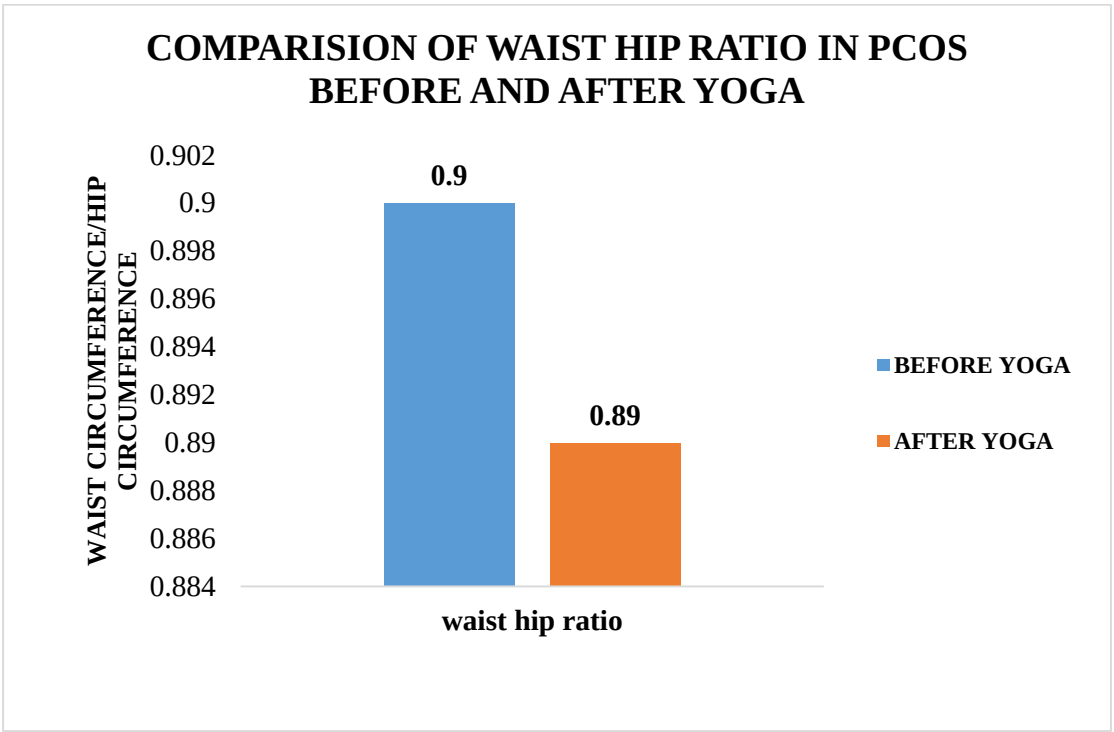

COMPARISION OF WAIST HIP RATIO IN PCOS BEFORE AND AFTER YOGA
0.902
0.9
0.898
0.896
0.894
0.892
0.89
0.888
0.886
0.884
WAIST CIRCUMFERENCE/HIP CIRCUMFERENCE
0.9
0.89
BEFORE YOGA
AFTER YOGA
waist hip ratio

TABLE NO:2					
COMPARISON OF WAIST HIP RATIO BEFORE AND AFTER YOGA					
VARIABLE	STUDY GROUP	N	MEAN	SD	P-VALUE
WAIST HIP ratio	BEFORE YOGA	30	0.90	0.062	**< 0.001*** **
	AFTER YOGA	30	0.89	0.054	

The mean values of Waist Hip ratio was found to be significantly reduced (p < **0.001)** in the study group following Yoga therapy.

TABLE NO:3					
COMPARISON OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE BEFORE AND AFTER YOGA					
VARIABLE	STUDY GROUP	N	MEAN	SD	P-VALUE
SYSTOLIC BP	BEFORE YOGA	30	111	6.68	**< 0.001*** **
	AFTER YOGA	30	105.27	4.44	
DIASTOLIC BP	BEFORE YOGA	30	68.80	5.91	**< 0.001*** **
	AFTER YOGA	30	64.73	3.66	

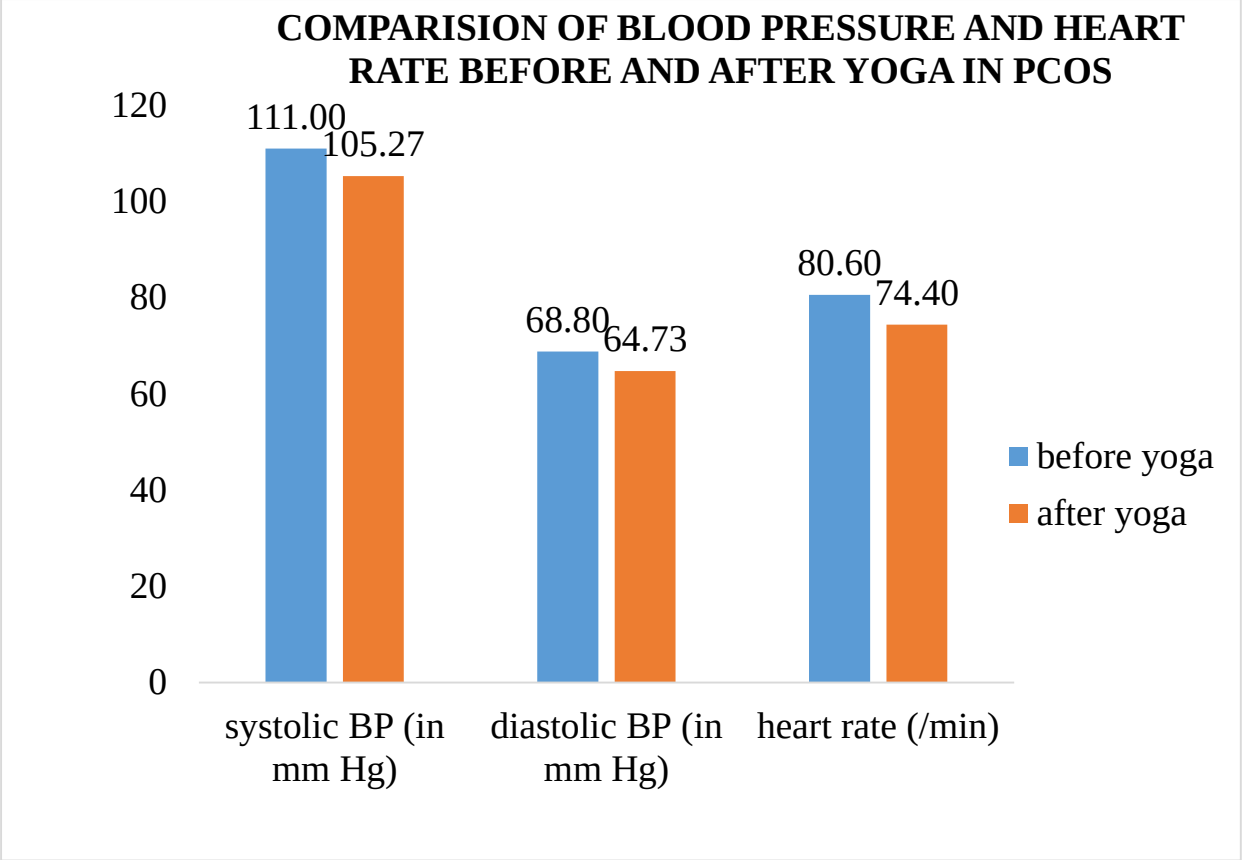
The mean values of blood pressure was found to be significantly reduced (p < **0.001)** in the study group following Yoga therapy.

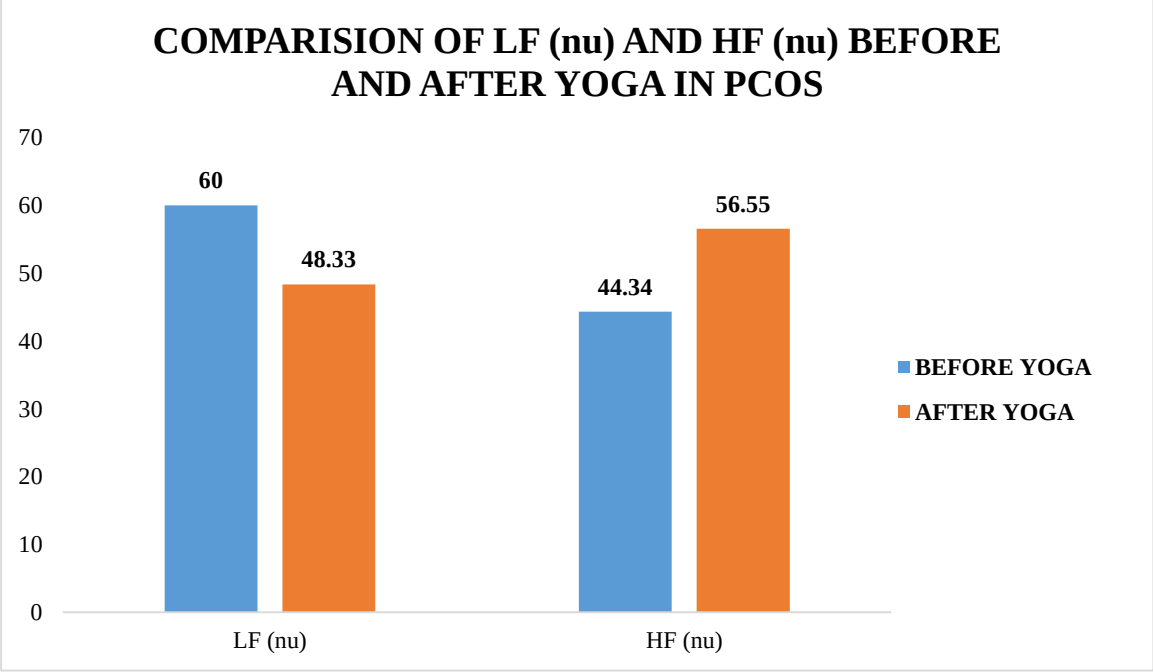
TABLE NO:4					
COMPARISON OF MEAN HEART RATE BEFORE & AFTER YOGA					
VARIABLE	STUDY GROUP	N	MEAN	SD	P-VALUE
MEAN HR	BEFORE YOGA	30	80.60	3.76	**< 0.001*** **
	AFTER YOGA	30	74.40	4.31	

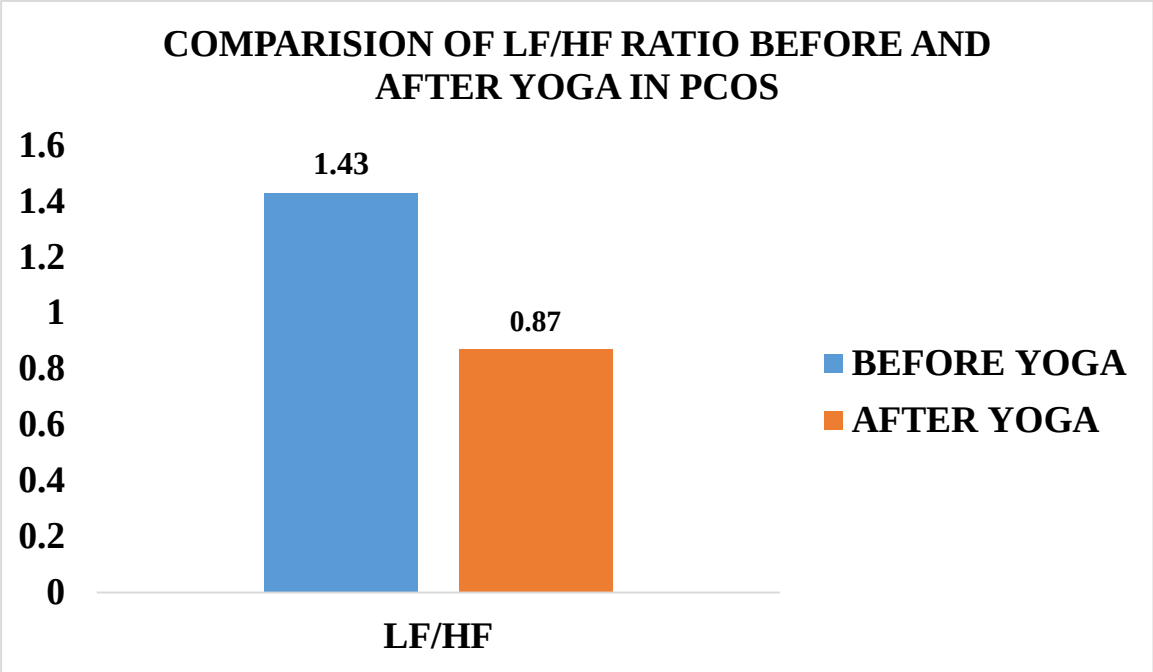
The mean values of Heart rate was found to be significantly reduced (p **< 0.001)** in the study group following Yoga therapy.

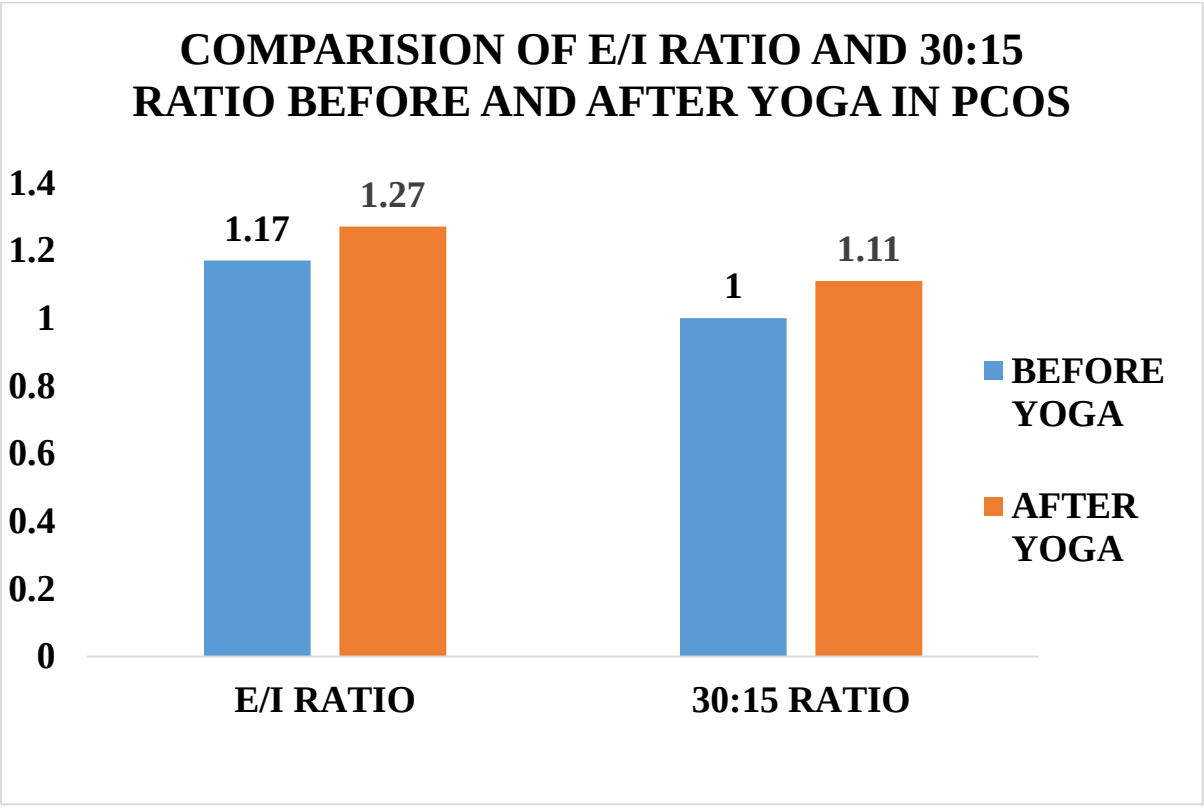
COMPARISION OF FREQUENCY DOMAINS

TABLE NO:5					
COMPARISON OF LF(nu) BEFORE AND AFTER YOGA					
VARIABLE	**STUDY GROUP**	**N**	**MEAN**	**SD**	**P-VALUE**
LF (nu)	BEFORE YOGA	30	60	7.54	**< 0.001*** **
	AFTER YOGA	30	48.33	7.13	
COMPARISON OF HF(nu) BEFORE AND AFTER YOGA					
HF (nu)	BEFORE YOGA	30	44.34	10.85	**< 0.001*** **
	AFTER YOGA	30	56.55	7.46	
COMPARISON OF LF/ HF RATIO BEFORE AND AFTER YOGA					
LF (nu) / HF (nu) RATIO	BEFORE YOGA	30	1.43	0.37	**< 0.001*** **
	AFTER YOGA	30	0.87	0.21	


COMPARISION OF BLOOD PRESSURE AND HEART RATE BEFORE AND AFTER YOGA IN PCOS
120
100
80
60
40
20
0
111.00
105.27
68.80
64.73
80.60
74.40
systolic BP (in mm Hg)
diastolic BP (in mm Hg)
heart rate (/min)
before yoga
after yoga


COMPARISION OF LF (nu) AND HF (nu) BEFORE AND AFTER YOGA IN PCOS
70
60
50
40
30
20
10
0
60
48.33
44.34
56.55
LF (nu)
HF (nu)
BEFORE YOGA
AFTER YOGA


COMPARISION OF LF/HF RATIO BEFORE AND AFTER YOGA IN PCOS
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1.43
0.87
LF/HF
BEFORE YOGA
AFTER YOGA


COMPARISION OF E/I RATIO AND 30:15 RATIO BEFORE AND AFTER YOGA IN PCOS
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1.17
1.27
1
1.11
E/I RATIO
30:15 RATIO
BEFORE YOGA
AFTER YOGA

The mean values of Frequency domains was found to be significantly improved (decrease in LF & LF/HF, increase in HF) (p **< 0.001)** in the study group following Yoga therapy.

COMPARISION OF AUTONOMIC FUNCTION BEFORE AND AFTER YOGA IN PCOS

TABLE NO:6

COMPARISON OF DEEP BREATHING TEST EXPIRATION / INSPIRATION RATIO BEFORE AND AFTER YOGA

VARIABLE	STUDY GROUP	N	MEAN	SD	P-VALUE
E/I RATIO	BEFORE YOGA	30	1.17	0.10	
	AFTER YOGA	30	1.27	0.09	**< 0.001*** **

The mean values of E/I ratio was found to be significantly improved (p **< 0.001)** in the study group following Yoga therapy.

TABLE NO:7

COMPARISON OF ORTHOSTATIC STANDING - 30/15 RATIO BEFORE AND AFTER YOGA

VARIABLE	STUDY GROUP	N	MEAN	SD	P-VALUE
30:15 RATIO	BEFORE YOGA	30	1.00	0.08	**< 0.001*** **
	AFTER YOGA	30	1.11	0.08	

The mean values of 30:15 ratio was found to be significantly improved (p < **0.001)** in the study group following Yoga therapy.

TABLE NO:8					
COMPARISON OF ORTHOSTATIC SYSTOLIC BLOOD PRESSURE BEFORE AND AFTER YOGA					
OST SYS BP	BEFORE YOGA	30	2.53	6.85	**< 0.001*** **
	AFTER YOGA	30	-2.93	4.32	
COMPARISON OF ORTHOSTATIC DIASTOLIC BLOOD PRESSURE BEFORE AND AFTER YOGA					
OST DBP	BEFORE YOGA	30	3.47	6.30	**< 0.001*** **
	AFTER YOGA	30	-2.07	3.46	

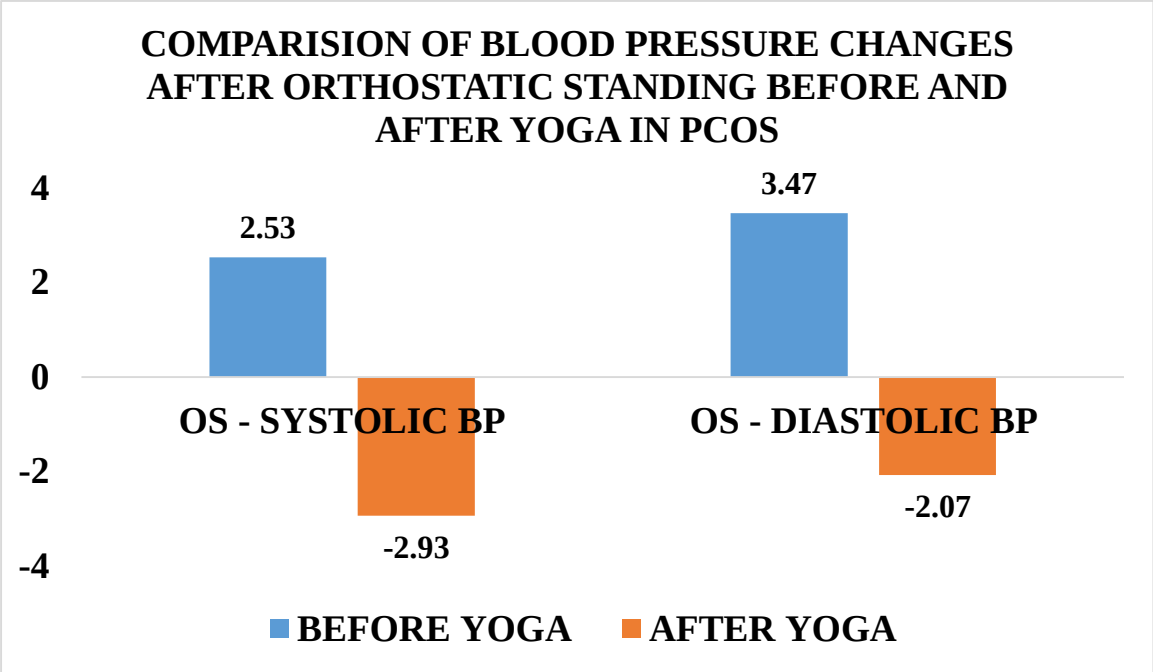
The mean values of BP in response to Orthostatic standing was found to be significantly reduced (p **< 0.001)** in the study group following Yoga therapy..

TABLE NO:9					
COMPARISON OF ISOMETRIC HAND GRIP SYSTOLIC AND DIASTOLIC BLOOD PRESSURE BEFORE & AFTER YOGA					
VARIABLE	STUDY GROUP	N	MEAN	SD	P-VALUE
IHG SYSTOLIC BP	BEFORE YOGA	30	9.40	2.84	**< 0.001****
	AFTER YOGA	30	6.73	2.38	
IHG DBP	BEFORE YOGA	30	14.87	3.05	**<0.001*****
	AFTER YOGA	30	10.13	2.29	

The mean values of Blood pressure in response to Isometric Handgrip was found to be significantly reduced (p **< 0.001)** in the study group following Yoga therapy.

TABLE NO:10					
COMPARISON OF PERCEIVED STRESS BEFORE & AFTER YOGA					
VARIABLE	STUDY GROUP	N	MEAN	SD	P-VALUE
PERCEIVED STRESS SCALE	BEFORE YOGA	30	21.8	5.77	**<0.001*****
	AFTER YOGA	30	13.3	3.84	

The mean values of stress score was found to be significantly reduced (p **< 0.001)** in the study group following Yoga therapy.


COMPARISION OF BLOOD PRESSURE CHANGES AFTER ORTHOSTATIC STANDING BEFORE AND AFTER YOGA IN PCOS
4
2
0
-2
-4
2.53
-2.93
3.47
-2.07
OS - SYSTOLIC BP
OS - DIASTOLIC BP
BEFORE YOGA
AFTER YOGA

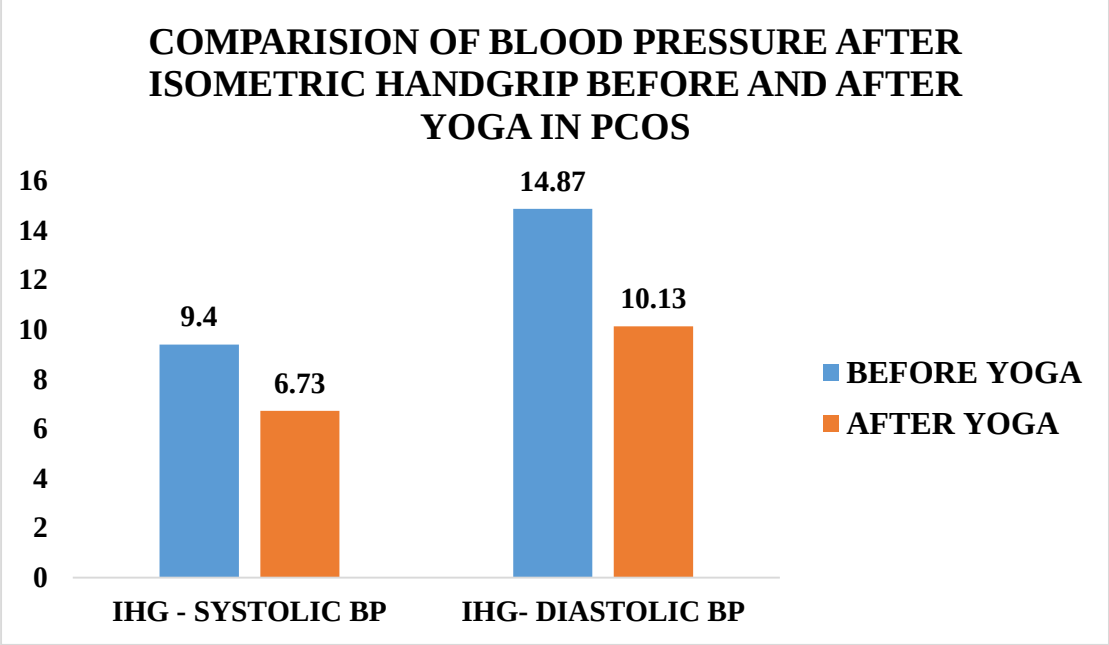

COMPARISION OF BLOOD PRESSURE AFTER ISOMETRIC HANDGRIP BEFORE AND AFTER YOGA IN PCOS
16
14
12
10
8
6
4
2
0
9.4
6.73
14.87
10.13
IHG - SYSTOLIC BP
IHG- DIASTOLIC BP
BEFORE YOGA
AFTER YOGA

TABLE NO:11

COMPARISON OF DEPRESSION BEFORE & AFTER YOGA

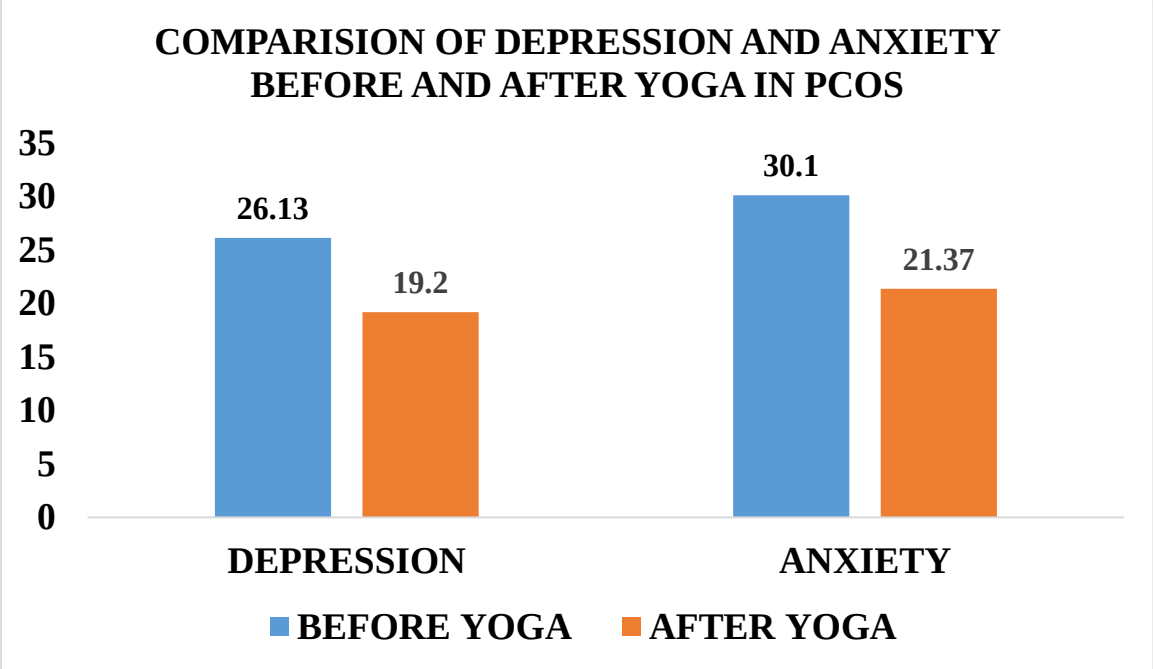
VARIABLE	STUDY GROUP	N	MEAN	SD	P-VALUE
DEPRESSION (BECKS SCORE)	BEFORE YOGA	30	26.13	3.69	**<0.001*** **
	AFTER YOGA	30	19.20	3.09	

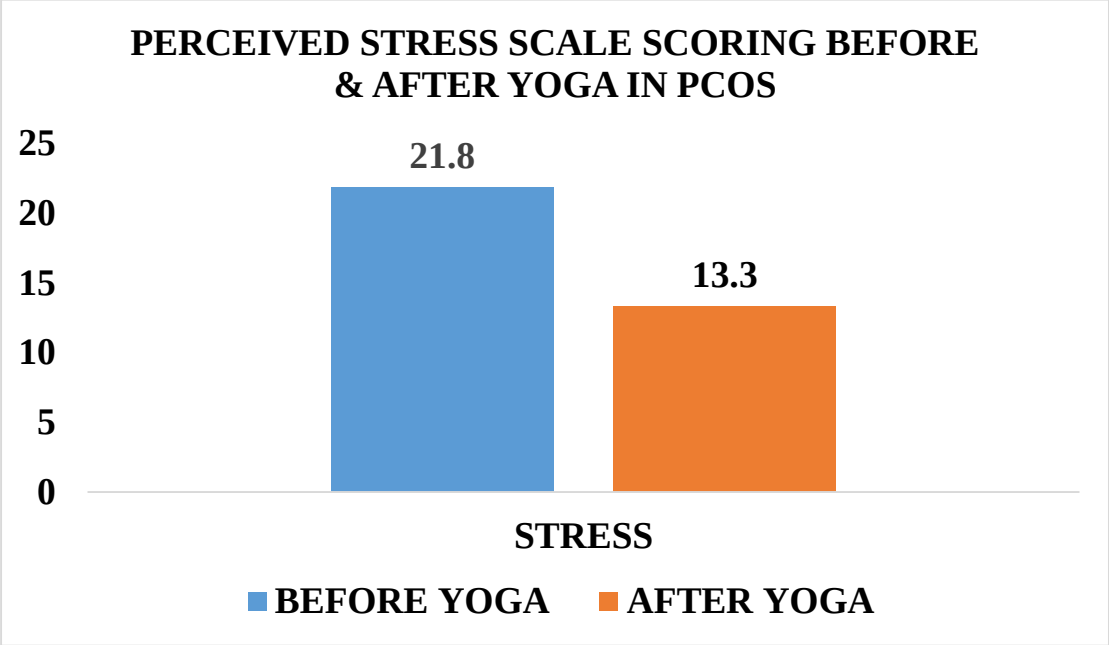
TABLE NO:12

COMPARISON OF ANXIETY BEFORE & AFTER YOGA

VARIABLE	STUDY GROUP	N	MEAN	SD	P-VALUE
ANXIETY (BECKS SCORE)	BEFORE YOGA	30	30.10	3.79	**< 0.001*** **
	AFTER YOGA	30	21.37	4.77	

The mean values of Depression and Anxiety were found to be significantly reduced (p **< 0.001)** in the study group following Yoga therapy.

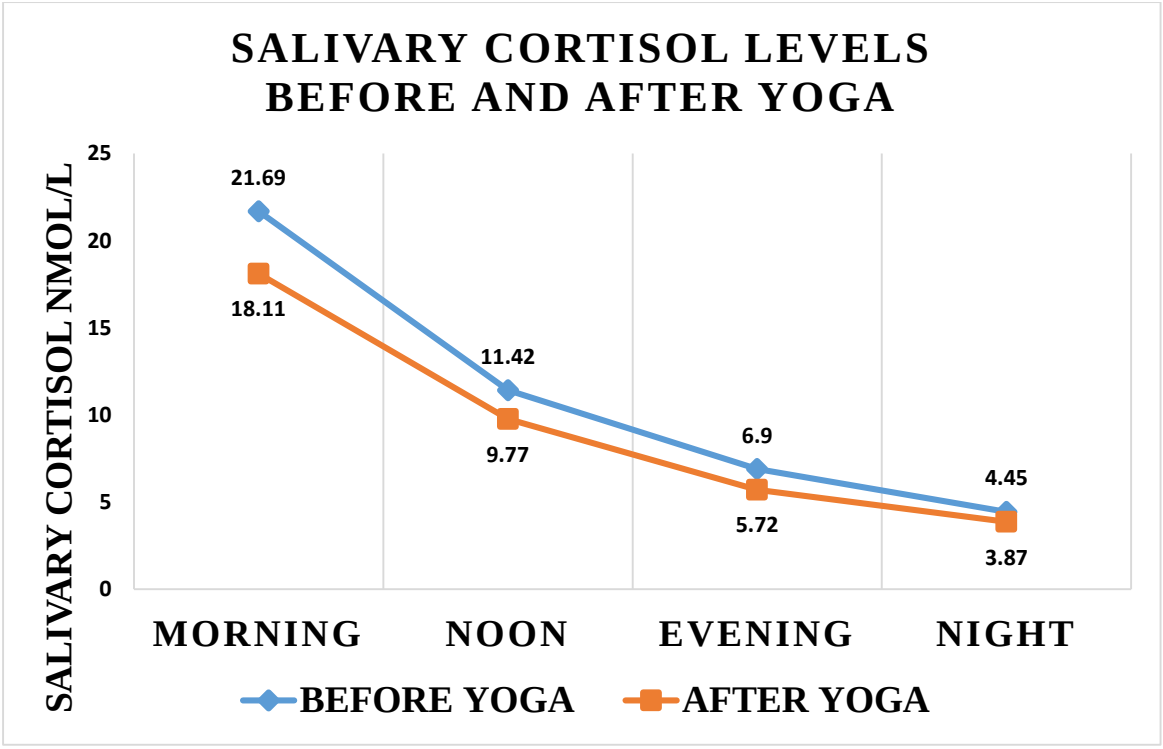

COMPARISION OF DEPRESSION AND ANXIETY BEFORE AND AFTER YOGA IN PCOS
35
30
25
20
15
10
5
0
26.13
19.2
30.1
21.37
DEPRESSION
ANXIETY
BEFORE YOGA
AFTER YOGA


PERCEIVED STRESS SCALE SCORING BEFORE & AFTER YOGA IN PCOS
25
20
15
10
5
0
21.8
13.3
STRESS
BEFORE YOGA
AFTER YOGA

SALIVARY CORTISOL

TABLE NO:13					
COMPARISON OF SALIVARY CORTISOL BEFORE & AFTER YOGA					
VARIABLE	STUDY GROUP	N	MEAN	SD	P-VALUE
SALIVARY CORTISOL (MORNING)	BEFORE YOGA	30	21.69	1.84	**<0.001*** **
	AFTER YOGA	30	18.11	1.57	
SALIVARY CORTISOL (NOON)	BEFORE YOGA	30	11.42	0.83	**<0.001*** **
	AFTER YOGA	30	9.77	1.26	
SALIVARY CORTISOL (EVENING)	BEFORE YOGA	30	6.90	0.52	**<0.001*** **
	AFTER YOGA	30	5.72	0.65	
SALIVARY CORTISOL (NIGHT)	BEFORE YOGA	30	4.45	0.73	**<0.001*** **
	AFTER YOGA	30	3.87	0.55	

The mean values of Salivary cortisol were found to be significantly reduced (p **< 0.001)** in the study group following Yoga therapy.


SALIVARY CORTISOL LEVELS
BEFORE AND AFTER YOGA
SALIVARY CORTISOL NMOL/L
25
20
15
10
5
0
21.69
18.11
11.42
9.77
6.9
5.72
4.45
3.87
MORNING
NOON
EVENING
NIGHT
BEFORE YOGA
AFTER YOGA

DISCUSSION

DISCUSSION

The present study was done to evaluate whether **Yoga therapy in Polycystic Ovarian syndrome** patients was effective in:

1. Improving the Autonomic dysfunction – using Heart rate Variability
2. Adrenal Fatigue – using perceived stress scale and Salivary cortisol estimation
3. Improving the Psychological emotional distress due to Anxiety and Depression – using Becks Anxiety Scale and Becks Depression Scale.

The asanas chosen for our study are those which are prescribed for PCOS patients and to improve the mental status. Duration was about 45mins-1hour per day for 90days. (Studies have shown the that minimum duration of Yoga to attain the beneficial effects was 6-12weeks)- ***Nagarathna R, et al.***

ANTHROPOMETRIC MEASUREMENTS:

Body Mass Index: The mean BMI of the PCOS group was 26.01 ± 3.89, 19 women are overweight or obese (BMI >25). **After 90days of regular Yoga therapy, the mean BMI (24.79 ±3.12) of the study population was significantly reduced.** Our study result was similar with ***Mahajan AS et al 1999***[300] reported 14 weeks of yoga therapy results in significant weight reduction in people who have the risk factors of developing Coronary artery disease.

Waist hip ratio (WHR): Mean WHR of our study group is 0.90 ± 0.06 **(obesity**). **After Yoga, significant reduction in WHR was observed**. This

was in accordance with ***Malhotra V, Singh S. et al 2005***[301] (40 days of yoga programme on Diabetic individuals resulted in decrease in BMI, WHR.

Possible mechanism for weight reduction and Waist Hip ratio:

1.Abdominal stretching during Yoga exercise leads to the regeneration of pancreatic cells, that in turn may increase utilization and metabolism of glucose in peripheral tissues, Liver and adipose tissues through enzymatic process[302, 303]. **2**. Expenditure of energy while performing Yoga. **3.** Reduction in stress and improvement in mental status by yoga reduces the over eating and regulates the satiety centre. **4**. Reduction of fat level in abdominal region is largely because of decrease in stress level by yoga which balances the HPA axis (stress, cortisol, binge eating, Abdominal fat deposition has strong correlation)[304, 305 , 306].

Resting cardiovascular parameters:

Mean Heart rate and Resting Blood pressure:

After yoga therapy there was a significant reduction in mean HR and Blood pressure of the PCOS. This tells about the reduction of sympathetic hyperactivity[307] after Yoga. This was in accordance with ***Sundar s et al.***[308] - 6 months of *Shavasana* practice decreases the Systolic and Diastolic blood pressure significantly in patients with essential Hypertension & **T.K Bera et al**[309] - *Shavasana* decreases Herat Rate and blood pressure.

The possible mechanism for the significant reduction of resting Heart rate and Blood pressure may be due to the benefits of Shavasana, which is the deep meditative state and gives relaxation. This reduces the anxiety and sympathetic

over activity which was caused by the stress. This in turn reduces the catecholamine synthesis which leads to peripheral vasodilatation and enhancement of peripheral circulation and hence reduction in diastolic BP. Yoga decreases the BMR and resting oxygen consumption. This leads to reduction in work load on heart which contributes to the reduction in heart rate and cardiac output. Thus systolic BP is reduced by Yoga[310, 311].

Autonomic Functions:

Analysis of frequency domain variable states that autonomic imbalance is present in the form of sympathetic over activity (high LF and LF/HF ratio) and decreased parasympathetic response in the form of vagal withdrawal (lower HF) in PCOS.

After 90days of Yoga therapy (comprising of Om chant, asanas and pranayama), there was a significant improvement in the frequency domains (LF decreased, LF/HF ratio decreased and HF increased). The shift toward Parasympathetic activity has occurred. This was similar with ***Vempati and Telles et al***[312]

Test for Sympathetic activity:

Orthostatic Standing test: (Blood pressure response to active standing):

The cardiovascular reflex changes on active standing after a period of rest in supine posture provides information on the integrity the baroreflex pathway. There occurs pooling of blood in the lower extremities on standing due to gravity which causes a reduced cardiac output and an immediate fall in BP. This is accompanied by an increase in heart rate which is recorded as a

maximum decrease in RR interval, a maximum at about the 15th beat. Contraction of the limb and abdominal vessels on active standing causes an increased venous return and a rise in BP which results in the slowing of heart rate which is recorded as an increase in RR interval a maximum at about the 30th beat (Borst et al).

From our study, we could find that after 1-3mins of active standing, the mean systolic BP of study group showed an increase of 2.53±6.85 mm hg. **Mean Diastolic BP of study group was increased** by 3.47±6.30 mm hg. This shows the *sympathetic hyperactivity*.

<u>After Yoga therapy</u>, mean systolic BP showed a fall of 2.93±4.32 mmHg and mean diastolic BP showed a fall of 2.07±3.46 mmHg. ***This was similar with Sahoo JK et al[313]. (by decreasing the sympathetic activity by reducing workload on heart)***

Isometric Hand grip (IHG):

The Diastolic blood pressure (DBP) changes following a sustained handgrip was recorded using a handgrip dynamometer. Most of the cases found it difficult to maintain the handgrip up to 5 minutes. So the test was limited to 3 minutes. The rise in diastolic BP just before the release of handgrip was significantly higher in the study group before yoga. The **rise in diastolic BP is a function sympathetic activity** due to the stimulation of baroreceptors and the peripheral vasoconstrictor fibres. The IHG DBP response shows an increased sympathetic activity in PCOS.

After Yoga therapy, **there was decreasing trend in the rise of DBP in response to IHG**. **This was in accordance with *udupa et al*[314] *(significant reduction in sympathetic hyperactivity after 3months of pranayama) and madanmohan et al*[315] *(shavasana decreases sympathetic response by decreasing the workload on heart)***

Test for Parasympathetic Activity:

Deep Breathing test:

This test is based on the principle of respiratory sinus arrhythmia. Heart rate increases during inspiration and decreases during expiration. E/I ratio ≥1.2 is considered normal for this age group (Ewing et al).

The E/I ratio in the PCOS group was **significantly lower** (Table 6). This is suggestive of decreased parasympathetic action or vagal withdrawal in PCOS.

After Yoga therapy, E/I ratio was significantly improved. This was in accordance with *Sarita Kanojia et al*[316].

Heart rate response to standing:

This test depends on integrity of afferent, centre and efferent of the baroreflex pathway. On standing, the pooling of blood in the lower extremities due to gravity causes a reduced cardiac output and an immediate fall in BP. This is accompanied by an increase in heart rate which is recorded as a decrease in RR interval, a maximum at about the 15th beat.

Contraction of the limb and abdominal vessels on active standing induces an increased venous return and a rise in BP. This results in the slowing of heart

rate which is recorded as an increase in RR interval a maximum at about the 30th beat.

30:15 ratio is a measure of vagal function. 30:15 ratio of the PCOS group was 1.00±0.08 which was significantly **lower** and suggests **vagal withdrawal**.

After yoga therapy, 30:15 ratio was significantly improved. 30:15 ratio & E/I ratio results are in accordance with *Pal GK, Velkumary S,et al*.[317]

Hence the decreased Parasympathetic function and increased sympathetic activity was noted in our study group at the time of Participation.

(Sympathovagal imbalance in PCOS was noted by saranya et al[318].)

After the intervention, shift towards parasympathetic activity was noted.

This was in accordance with ***Sarita Kanojia et al 2013[319] & Streeter CC et al*** 2012[320]. Overall effect of Yoga is to bring the Parasympathetic dominance, eventhough individual asana has different effects[321].

The possible mechanism in the improvement of Autonomic function and stress reduction may be due to:

1. **Ujjayi Pranayama (Ocean Breath)** - one of the method of resistance breathing that produces laryngeal contracture and partial closure of glottis to hinder the flow of air. Resistance breathing techniques elevates intrathoracic pressure, baroreceptor stimulation, respiratory sinus arrhythmia (RSA), and HRV[322]. Using breath-holds with Ujjayi increases PNS activity[323]. '**Om' chant** involves slow breathing, airway resistance (contracting the vocal cords to generate sound), which

increase vagal tone and physiologic relaxation[324]. ***Shavasana blunt the sympathetic activity by decreasing workload on heart.***

2. **Pranayama, stretches the lung tissue producing inhibitory signals from action of slowly adapting receptors (SAR). Hyperpolarising currents are produced in high amount from the fibroblast (connective tissue) (this is due stretching effect of pranayama). Hyperpolarizing currents is linked with Parasympathetic activity and relaxation of vascular smooth muscle[325]. These inhibitory signals coming from cardiorespiratory region involving vagi are believed to synchronize neural elements in the brain leading to changes in autonomic nervous system and a resultant condition characterized by reduced metabolism and parasympathetic dominance[326].**
3. **Yoga leads to an inhibition of posterior or sympathetic area of Hypothalamus.** This inhibition regulates body's sympathetic activity to stressful stimuli and restores autonomic regulatory reflex mechanisms associated with stress. Yoga inhibit the areas responsible for fear, aggressiveness and rage, and stimulate the rewarding pleasure centres in the median forebrain and other areas leading to a state of bliss and pleasure. This inhibition results in lower anxiety, heart rate, respiratory rate, blood pressure[327, 328, 329.]
4. Asanas comes under the low intensity and non-vigorous exercises that act on HPA axis positively lowers the sympathetic stimulation and

significantly decreases the production and discharge of catecholamines with respect to stress[330].

5. Yoga practice act on limbic system (one of the higher centre for ANS) and controls homeostasis by ANS-Endocrine modulation[331].
6. yoga may increase the hippocampal and right amygdala activation and increase in parasympathetic response through right ventromedial hypothalamic stimulation[332]

Psychological Parameters:

Anxiety:

Scoring system done in our study group shown moderate anxiety levels. **After Yoga Anxiety score was significantly reduced** this was in accordance with **Ram nidhi et al & Vempati RP, Telles S.et al 2002**.

*Reduction of stress by regulation of sympathetic activity[333] leads to decrease in anxiety[334]. **After the yoga practice**, Calmness of mind enables greater awareness by changing the individual's cognition and perceived self-efficacy with respect to stress inducing factors[335], hence decreases the anxiety levels.*

Depression:

In our study Mean Score among the PCOS comes under moderate depression. **After 90 days of Yoga the mean depression among study group was significantly reduced**. Our results are in accordance with ***Telles S, Nagarathna R et al. 1995[336] & Ram Nidhi et al.*** *Thus Yoga reduces the depression levels, the reason may be due to **yoga breathing which stimulates parasympathetic activity, which in turn promotes the GABA ergic activity***

related with improved mood. This was in accordance with **Streeter CC** ***et al*** *(Yoga therapy for 12weeks leads to high thalamic GABA levels)*[337].

Stress, salivary cortisol and adrenal fatigue:

In our study **Cohen perceived stress scale and salivary cortisol estimation** were performed to diagnose the stress in PCOS and thus Adrenal fatigue was evaluated.

Mean score was 21.8 ± 5.7, score of above 20 is considered as higher stress. This shows that our study group has been influenced by stress. These results are similar with **Eggers S, Kirchengast S. et al.** reported that stress is one of the additional risk factors in the development of PCOS and. **After 90 days of Yoga therapy, mean score was 13.3±3.8, significant reduction in the stress levels**. These results are in accordance with Latha and Kaliappan K 1991[338] Sahajpal P and Ralte R 2000[339]. Ram Nidhi et al reported that adolescents with PCOS had significantly higher amount of perceived stress and Integrated Yoga therapy for 90 days significantly reduced the stress level than the adolescents with regular exercise.

Cortisol secretion follows the circadian rhythm. So that morning, noon, evening and midnight salivary cortisol level were estimated. Our study results showed ***higher basal cortisol levels.*** This was in accordance with **Luciana Tock et al.** As **Nidhi et al**, reported, our study reveals there is an increased stress among PCOS. Thus the prevalence of stress (psychological, emotional distress) & high sympathetic activity in patients with PCOS might be the

reason for higher basal salivary cortisol and altered circadian pattern. (Results from Cohen perceived stress scale, supports the above said findings)

And these findings showed that the study population might be in the ***stage of Resistance*** (Hans selye General adaptation syndrome to stress).

According to Dr. James L.Wilson (mentioned in his book Adrenal Fatigue, the 21st century syndrome (p.no 297))[340]. On exposure to stress, according to human response, stages of adrenal fatigue has stated. Study Population might belong to ***Repeated partial recovery followed by recurring Adrenal Fatigue***. Stress reduction therapy is more in favour of non-pharmacological approach like Yoga. Therefore our study group subjected to Yoga for 90days. *Mean salivary cortisol Results fall under the normal range after yoga therapy.* This was in accordance with Ross A et al 2010[341].

Possible reason for decrease in salivary cortisol and stress score → *Yoga reduces stress arousal by modulating sympathetic nerve activity and reducing anxiety levels (Telles S, Gaur V, Balkrishna A et al 2009)* *Yoga reduces the perceived stress through the cerebrohypothalamic or corticolimbic pathway[342] by inducing the cortical areas that affect the neurotransmitter and hormonal release[343].*

As salivary cortisol and stress scores have returned to the normal basal levels, it shows that the study population are improving from the state of Repeated partial recovery (pattern 3) and thus preventing from the entry into the final stage of exhaustion or Adrenal fatigue. However, long term follow up studies are needed to study the course of Adrenal fatigue.

CONCLUSION

CONCLUSION

Yoga is an ancient Indian Medicine. A form of holistic approach which incorporates a person's somatic, psychological, spiritual constituents to bring the positive effect on health especially stress related disorders.

Results of this present study concludes that regular practice of yoga improves the autonomic dysfunction and brings the parasympathetic effect, produces weight reduction (decrease in BMI & WHR), lowers the psychological parameters which are common in PCOS such as anxiety, depression and Stress, decreases the salivary cortisol levels.

According to their stress& salivary cortisol levels adrenal fatigue was evaluated. As Adrenal fatigue has different phases, our study group belongs to the resistance stage, (*Repeated partial recovery followed by recurring Adrenal Fatigue*). Presence of stress due to their physical features may further deteriorate their HPA axis and may lead into the adrenal exhaustion stage if the stress persists. Stress reduction in the form of yoga may prevent the further complications of stress in PCOS.

By practising regular yoga, person can be treated and prevented from the chronic complications of PCOS without any risk and stress reduction can be achieved.

Hence yoga, can be included as a treatment modality, adjunctive to pharmacotherapies that are currently in use.

Limitations of the study

Our study was done in a smaller sample size. To substantiate our findings and apply it to general population studies using larger sample size is essential. All the PCOS women were selected from medical endocrine clinic. So in order to generalize the findings, larger studies including all phenotypes of PCOS should be conducted. Direct measurements of the sympathetic system (catecholamine levels) were not evaluated in our study. Biomarker for Anxiety and Depression were not evaluated in this study. Yoga therapy was not compared with controls (other treatment modalities like Exercise, Diet modification and pharmacological therapy). Hormones like mineralocorticoids and sex steroids which are all secreted from adrenal gland should be evaluated in future studies. Further long term follow up is recommended to study the functional status of adrenal and nature of adrenal fatigue.

SUMMARY

SUMMARY

A study was conducted to evaluate the effect of Yoga therapy on autonomic function and adrenal fatigue (estimation of salivary cortisol levels & Cohen perceived stress score) in patients with polycystic ovarian syndrome.

30 PCOS patients were participated in the study & they were given Yoga therapy (specific for PCOS) for 45mins -1hour / day for 3months with a break after every 6 days (protocol designed by Department of Yoga & Naturopathy) Before and after the therapy, subjects underwent Autonomic function tests, stress levels were assessed by Cohen perceived stress scale and salivary cortisol levels (4 samples), depression and anxiety were assessed by Becks Depression scale and Becks Anxiety scale respectively.

The results showed a significant reduction in weight and WHR) and moderate levels of depression and anxiety were present at the time of participation, after Yoga significantly reduction was observed. Sympathetic over activity was shifted towards parasympathetic activity after Yoga. Adrenal fatigue was evaluated patients were in resistance phase (*Repeated partial recovery followed by recurring Adrenal Fatigue*) at the time of participation (stress score were high & salivary cortisol higher basal levels). Significant reduction in stress levels after the therapy, preventing the entry into fatigue (final exhaustion phase). Hence PCOS is associated with stress (Adrenal fatigue), autonomic and psychological disturbances. Regular yoga therapy showed an improvement in this condition. Hence, YOGA, a novel approach, can be used in treating PCOS without any adverse effects.

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ANNEXURES

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.K.Nathiya
Postgraduate M.D. (Physiology)
Madras Medical College
Chennai 600 003

Dear Dr. K.Nathiya,

The Institutional Ethics Committee has considered your request and approved your study titled **"Evaluation of effect of Yoga on an autonomic function and adrenal fatigue in polycystic ovarian syndrome" No.26082015.**

The following members of Ethics Committee were present in the meeting held on 04.08.2015 conducted at Madras Medical College, Chennai-3.

1.	Prof.C.Rajendran, M.D.,	: Chairperson
2.	Prof.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3.	Prof.Sudha Seshayyan, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4.	Prof.B.Vasanthi, M.D., Professor Pharmacology, MMC	: Member
5.	Prof.A.Rajendran, M.S., Professor, Inst.of Surgery, MMC	: Member
6.	Prof.Saraswathy, M.D., Director, Inst. Of Pathology, MMC	: Member
7.	Prof.Srinivasagalu, Director, Inst.of Inter Med. MMC	: Member
8.	Tmt. J.Rajalakshmi, J.A.O. MMC, Ch-3	: Lay Person
9.	Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
10.	Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

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 patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

ஆராய்ச்சி தகவல் தாள்

ஆராய்ச்சி தலைப்பு

அட்டனாமிக் நரம்புமண்டல மாற்றங்களையும், இதயத்துடிப்பு வேறுபடுதலையும், அட்ரினல் சுரப்பியின் சோர்வை உமிழ்நீர் கார்டிசால் ஹார்மோன் கொண்டு ஆராய்தலையும், சினைப்பையில் நீர்கட்டி உள்ள இளம் பெண்களுக்கு யோகா பயிற்சி அளித்து கண்டறிதல்.

பெயர் :

வயது :

ராஜீவ் காந்தி அரசு பொது மருத்துவமனைக்கு வரும் சினைப்பையில் கட்டி உள்ள இளம் பெண்களுக்கு யோகா பயிற்சி 12 வாரங்கள் அளித்து அட்டனாமிக் நம்பு மண்டல மாற்றங்களையும், இதயத்துடிப்பு வேறுபடுதலையும், அட்ரினில் சுரப்பியின் சோர்வை உமிழ்நீர் கார்டிசால் ஹார்மோன் கொண்டு பரிசோதனை செய்யும் ஆய்வு இங்கு நடைபெறுகிறது.

சினைப்பையில் நீர் கட்டி உள்ள இளம் பெண்களுக்கு அட்டனாமிக் நரம்பு மண்டலத்தில் ஏற்படும் மாற்றங்களால் இருதய சம்பந்தமான பிரச்சனைகள் பரவலாக காணப்படுகிறது. அதனால் அட்டனாமிக் நரம்பு மண்டலத்தில் ஏற்படும் மாற்றங்களை இதயத்துடிப்பு வேறுபடுதல் மூலமும், மன அழுத்தத்தின் தன்மைக்கு ஏற்பட உமிழ்நீர் கார்டிசால் ஹார்மோன் மாறுபடுதலையும் மேலும் யோகா பயிற்சி சினைப்பை நீர் கட்டி நோயின் தன்மையை எந்த அளவிற்கு குணமாக்குகிறது என்பதையும் இந்த சிறப்பு பரிசோதனை மூலம் எளிதில் கண்டறிய முடியும் என்பதே இந்த ஆய்வின் நோக்கமாகும்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இதில் தங்களது அட்டனாமிக் நரம்பு மண்டல சோதனை மற்றும் உமிழ்நீர் கார்டிசால் ஹார்மோன் அளவு போன்ற சிறப்பு பரிசோதனை செய்து அதன் தகவல்களை ஆராய்வோம். இந்த ஆய்வு தங்களது அன்றாட செயல்பாடுகளை பாதிக்காது என்று தெரிவித்துக்கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆய்வின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக்கொள்கிறேம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின்போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின்பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

நாள் :

இடம் :

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சி தலைப்பு
அட்டனாமிக் நரம்புமண்டல மாற்றங்களையும், இதயத்துடிப்பு வேறுபடுதலையும், அட்ரினல் சுரப்பியின் சோர்வை உமிழ்நீர் கார்டிசால் ஹார்மோன் கொண்டு ஆராய்தலையும், சினைப்பையில் நீர்கட்டி உள்ள இளம் பெண்களுக்கு யோகா பயிற்சி அளித்து கண்டறிதல்.

பெயர் :

வயது :

பங்குபெறுபவரின் அடையாள எண் :

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கமும் முழுமையாக எனக்குத் தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு நான் எனது சம்மதத்தைத் தெரிவிக்கிறேன்.

எனது அட்டனாமிக் நரம்பு மண்டலத்தில் ஏற்படும் மாற்றங்களை இருதய துடிப்பு வேறுபாடுதல் மூலம் அறிதல் மற்றும் உமிழ்நீர் கார்டிசால் ஹார்மோன் அளவு கண்டறிதல் மற்றும் 12 வாரங்கள் யோகா பயிற்சிக்கு தொடர்ந்து வர எனக்கு சம்மதம்.

இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின்வாங்கலாம் என்பதை புரிந்துகொண்டேன். நான் சினைப்பையில் நீர் கட்டி குறித்த இந்த ஆராய்ச்சியின் விவரங்கள் கொண்ட தகவல் தாளைப் பெற்றுக்கொண்டேன். அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்துகொண்டேன்.

உமிழ்நீர் கார்டிசால் ஹார்மோன் அளவை பரிசோதிக்க சம்மதிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின்பேரில் பங்கு பெறுகின்றேன்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

நாள் :

இடம் :

INFORMED CONSENT FORM

Title of the study: "**Evaluation of effect of yoga on Autonomic functions and adrenal fatigue in Polycystic Ovarian Syndrome"**

Name of the Participant:

Name of the Principal Investigator: Dr.K.Nathiya

Name of the Institution:

Institute of Physiology and Experimental Medicine,

Madras Medical College and Govt. General Hospital,

Chennai - 3

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 yoga on Autonomic functions and adrenal fatigue in Polycystic Ovarian Syndrome** patients"

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 understand 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_____

PROFORMA

PCOS Symptom Check List			
PERSONAL INFORMATION			
1	Name		
2	Age		
3	Date of Birth		
4	Address		
5	Contact no		
ANTHROPOMETRIC MESAURES			
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	
15		Alopecia	
16		Hirsutism	

Past history:

History of any drug intake

History of yoga practice, regular exercise

History of Psychiatric illness like Anxiety, Depression

History of associated illness:

a. Diabetes

b. Hypertension

c. Any Heart disease

d. Respiratory diseases

e. Hypothyroidism

EXAMINATION

General examination:

Pulse rate:

Blood pressure:

Systemic examination:

Cardiovascular system:

Respiratory system:

Resting Heart Rate Variabilty:

AUTONOMIC FUNCTIONS TESTS

1. Basal Recording Heart Rate :

Blood Pressure :

2. Resting HRV

LF :

HF :

LF/HFratio :

3. Deep Breathing E/I ratio :

4. Orthostatic Standing Test:

30/15 ratio:

B.P. (2 minutes):

B.P (5minutes):

5. Isometric Handgrip: Heart rate (1minute):

Heart rate (5minutes):

BP (2minutes):

BP (5minutes):

Investigations:

1. Salivary Cortisol
2. Transvaginal/transabdominal Ultrasound
3. Thyroid profile

SCORING SCALE

1. Cohen Perceived stress scale
2. Becks Anxiety Scale
3. Becks Depression Scale

BEFORE YOGA

S. No	AGE	SEX	Ht	Ht^2	Wt	BMI	Waist	Hip	WHR	SBP	DBP	Mean HR	LF	HF	LF/HF	OST 30/15 ratio	OST SBP_1	OST DBP1	E/I ratio	IHG SBP	IHG DBP	Stress	Beck-Depression	B-anxiety	salivary cortisol (nmol/l)			
	Yr	M/F	m	m^2	Kg	kg/m^2	cm	cms	cm	mm Hg	mm Hg	Per min	nu	nu											8 am	1 pm	5 pm	12 am
1	20	F	1.54	2.37	63	26.56	82	95	0.86	106	64	80	65.8	40.3	1.63	1.01	-8	6	1.02	12	16	25	22	29	22	11.8	7.12	3.4
2	22	F	1.6	2.56	62	24.22	79	90	0.88	110	64	84	49.8	37.7	1.32	0.97	4	8	1.15	6	12	19	28	34	21.5	11.5	6.9	2.9
3	19	F	1.52	2.31	60	25.97	81	94	0.86	100	66	82	58.5	49.7	1.18	1.06	8	4	1.24	12	20	23	25	28	23.2	11.79	7.4	3.08
4	21	F	1.56	2.43	64	26.30	78	91	0.86	114	60	76	51.6	41.2	1.25	1.02	16	10	1.18	6	14	19	27	30	21.92	10.1	6.74	4.1
5	24	F	1.55	2.40	62	25.81	84	94	0.89	110	70	76	66.2	51.4	1.29	1.01	6	12	1.2	10	16	24	24	35	23.41	11.2	7.13	4.5
6	20	F	1.57	2.46	66	26.78	82	90	0.91	108	62	84	58.2	67.5	0.86	1.21	18	8	1.34	14	12	17	29	22	22.11	12.3	6.95	4.76
7	23	F	1.62	2.62	58	22.10	80	93	0.86	118	72	80	58.6	38.5	1.52	0.97	6	12	1.12	8	16	28	24	28	23.76	11.31	7.27	4.04
8	21	F	1.58	2.50	57	22.83	80	90	0.89	110	60	80	62.4	46.7	1.34	1.02	2	4	1.06	8	16	19	29	26	19.8	11.03	5.8	3.24
9	26	F	1.6	2.56	69	26.95	81	93	0.87	112	74	76	68.7	39.2	1.75	0.98	18	8	1.18	10	12	20	27	33	21.63	12.08	7.01	4.4
10	23	F	1.62	2.62	50	19.05	76	92	0.83	120	70	84	53.4	33.8	1.58	1.01	-4	-2	1.2	8	18	10	18	22	16.7	9.45	5.89	3.41
11	24	F	1.63	2.66	54	20.32	79	92	0.86	106	64	78	61.9	37.6	1.65	0.88	-2	-4	1.12	6	12	12	22	30	21.8	12.6	6.45	4.9
12	22	F	1.65	2.72	70	25.71	83	94	0.88	100	60	82	55.3	68	0.81	1.04	-4	-4	1.42	10	14	28	29	26	22	12.12	7.21	5.21
13	24	F	1.54	2.37	68	28.67	96	102	0.94	118	78	86	67.8	34.9	1.94	0.9	2	6	1.19	6	20	18	28	32	21.2	11.56	7.59	4.19
14	25	F	1.56	2.43	50	20.55	74	88	0.84	120	66	80	59.6	36.2	1.65	0.85	-2	2	1.04	16	16	23	21	29	21.97	12	7.7	4.85
15	21	F	1.52	2.31	56	24.24	81	92	0.88	102	68	84	67.4	38.2	1.76	1.02	-4	-2	1.21	10	18	19	29	31	19.86	10.32	7.11	4.69

BEFORE YOGA

S. No	AGE	SEX	Ht	Ht^2	Wt	BMI	Waist	Hip	WHR	SBP	DBP	Mean HR	LF	HF	LF/HF	OST 30/15 ratio	OST SBP_1	OST DBP1	E/I ratio	IHG SBP	IHG DBP	Stress	Beck-Depression	B-anxiety	salivary cortisol (nmol/l)			
	Yr	M/F	m	m^2	Kg	kg/m^2	cm	cms	cm	mm Hg	mm Hg	Per min	nu	nu											8 am	1 pm	5 pm	12 am
16	25	F	1.66	2.76	80	29.03	107	110	0.97	110	74	88	65.2	32.5	2.01	1.05	-6		1.16	14	16	27	29	34	22.67	11.05	6.99	5.86
17	23	F	1.53	2.34	69	29.48	113	118	0.96	114	62	80	67.8	40.5	1.67	0.89	4	8	1.05	8	18	22	28	34	23	12.01	7.32	4.43
18	25	F	1.55	2.40	52	21.64	84	96	0.88	100	66	74	45.3	74.2	0.61	1.19	8	10	1.42	6	16	9	19	22	19.43	9.21	5.97	3.94
19	20	F	1.58	2.50	75	30.04	113	115	0.98	114	74	84	65.1	42.7	1.52	1.03	-4	-8	1.1	10	12	29	30	33	22.81	11.69	7	4.06
20	22	F	1.56	2.43	70	28.76	105	112	0.94	112	74	80	68.3	43.2	1.58	0.97	-2	-4	1.14	8	16	24	25	32	24.1	12.01	7.27	5.47
21	23	F	1.54	2.37	73	30.78	112	107	1.05	120	78	86	61.6	36.8	1.67	1.04	4	6	1.22	10	14	31	30	34	22.07	10.69	7.08	5.63
22	25	F	1.58	2.50	72	28.84	99	103	0.96	116	70	82	63.2	33.1	1.91	1.01	-4	-2	1.09	14	18	30	27	30	21.6	12.35	6.99	4.51
23	26	F	1.68	2.82	54	19.13	76	92	0.83	106	62	72	44.6	60.8	0.73	0.94	2	4	1.17	6	12	18	20	29	18.41	11.06	6.03	4.93
24	20	F	1.56	2.43	70	28.76	109	111	0.98	114	74	78	65.6	51.2	1.28	0.98	-4	-4	1.08	8	12	23	28	35	22.71	12	7.11	4.02
25	23	F	1.55	2.40	56	23.31	80	98	0.82	110	64	80	43.3	50.6	0.86	1.03	4	6	1.32	6	16	20	21	29	17.48	11.22	5.85	4.76
26	22	F	1.53	2.34	76	32.47	108	106	1.02	120	80	84	66.5	48.6	1.37	0.87	8	10	1.2	8	20	26	31	31	24.02	10.72	7.31	5.01
27	23	F	1.65	2.72	58	21.30	75	94	0.80	116	68	76	60.2	38.5	1.56	0.99	-4	-2	1.18	12	12	22	26	27	21.04	12.03	6.61	4.34
28	21	F	1.52	2.31	64	27.70	88	96	0.92	104	70	80	57.4	39.7	1.45	1.02	4	8	1.15	10	8	17	29	31	22.99	12.25	7.08	4.84
29	24	F	1.62	2.62	79	30.10	108	113	0.96	100	76	82	68.1	35.3	1.93	1	2	-2	1.03	8	10	21	29	35	21.87	11.3	7.16	4.87
30	25	F	1.58	2.50	82	32.85	112	116	0.97	120	74	80	52.5	41.6	1.26	0.98	8	14	1.19	12	14	32	30	32	23.69	11.78	7	5.02

AFTER YOGA

S. NO	AGE yrs	SEX (M/F)	Ht (m)	Ht^2 m^2	Wt kg	BMI kg/m^2	Waist (cms)	HIP cm	WHR	SBP (mm Hg)	DBP (mm Hg)	Mean HR (/min)	LF nu	HF nu	LF/HF	OST 30/15 ratio	OST SBP_1	OST DBP_1	E/I ratio	IHG SBP	IHG DBP	stress	Becks depression	anxiety	Salivary cortisol nmol/l			
																									8 am	1 pm	5 pm	12 am
1	20	F	1.54	2.37	61	25.72	82	95	0.86	106	60	74	38.6	56.5	0.68	1.05	-6	-4	1.19	10	12	11	14	20	15.6	9.08	5.98	3.01
2	22	F	1.6	2.56	59	23.05	79	90	0.88	100	60	70	40.9	63.5	0.64	1.08	-4	0	1.23	8	8	17	21	23	17.04	9.17	6.01	2.89
3	19	F	1.52	2.31	55	23.81	81	94	0.86	100	64	78	49.6	50.1	0.99	1.07	-2	-4	1.24	0	10	21	16	20	21.1	11.6	7.2	3.01
4	21	F	1.56	2.43	60	24.65	78	91	0.86	110	66	72	43.2	53.7	0.80	1.1	-2	-2	1.18	8	6	16	20	18	20.42	7.4	5.44	4
5	24	F	1.55	2.40	59	24.56	84	94	0.89	104	62	74	47.8	59.6	0.80	1.09	-4	-2	1.2	8	12	12	16	24	18.21	10.64	6.32	3.45
6	20	F	1.57	2.46	62	25.15	80	90	0.89	108	64	70	51.4	68.3	0.75	1.2	-8	-6	1.36	8	12	9	19	13	17.08	10.97	6	4.14
7	23	F	1.62	2.62	55	20.96	80	93	0.86	104	70	78	32.4	48.6	0.67	1	-10	2	1.28	10	8	15	17	18	18.79	8.46	6.2	3.12
8	21	F	1.58	2.50	53	21.23	79	90	0.88	100	60	80	45.5	62.1	0.73	1.05	-2	-2	1.22	12	14	13	22	17	16.32	10.56	5.4	3.02
9	26	F	1.6	2.56	67	26.17	80	93	0.86	106	66	76	50.4	58.2	0.87	1.17	-4	4	1.32	6	10	8	19	24	17.41	9.97	4.01	3.87
10	23	F	1.62	2.62	50	19.05	76	92	0.83	110	62	80	44.8	61.7	0.73	1.23	-8	2	1.23	8	8	10	16	14	15.72	7.21	4.34	2.89
11	24	F	1.63	2.66	52	19.57	79	92	0.86	106	64	76	51.1	55.9	0.91	1.19	-2	-4	1.35	6	6	14	18	13	18.56	9.76	5.12	4.1
12	22	F	1.6	2.56	65	25.39	83	94	0.88	100	60	72	47.3	68	0.70	1.25	-4	-2	1.48	8	10	12	21	17	19.31	8.57	6.41	4.22
13	24	F	1.54	2.37	64	26.99	93	102	0.91	104	70	80	46.7	57.2	0.82	1.17	-8	-4	1.25	4	12	15	17	26	18.47	8.02	4.94	3.23
14	25	F	1.56	2.43	52	21.37	74	88	0.84	112	66	72	48.5	66.4	0.73	1.09	-2	-4	1.21	6	8	8	20	19	17.06	11.45	5.78	3.98
15	21	F	1.52	2.31	56	24.24	79	91	0.87	102	64	84	45.2	58.2	0.78	1.13	-6	-8	1.33	8	14	17	22	22	18.21	7.95	6.23	4.41

AFTER YOGA

S.NO	AGE	SEX	Ht	Ht^2	Wt	BMI	Waist	HIP	WHR	SBP	DBP	Mean HR	LF nu	HF nu	LF/HF	OST 30/15 ratio	OST SBP_1	OST DBP_1	E/I ratio	IHG SBP	IHG DBP	stress	Becks depression	anxiety	Salivary cortisol nmol/l			
	yrs	(M/F)	(m)	m^2	kg	kg/m^2	(cms)	cm		(mmHg)	(mmHg)	(/min)													8am	1pm	5pm	12 am
16	25	F	1.66	2.76	74	26.85	106	110	0.96	110	68	70	53.1	42.7	1.24	1.06	-2	-2	1.4	4	12	13	20	25	17.81	8.76	5.72	5
17	23	F	1.53	2.34	60	25.63	111	118	0.94	106	62	66	44.3	62.7	0.71	1.15	-4	-6	1.23	8	8	18	24	28	19.59	9.37	5.47	4.21
18	25	F	1.55	2.40	51	21.23	84	96	0.88	100	66	74	45.7	75.2	0.61	1.2	-8	-4	1.44	6	10	7	13	15	15.07	8.86	4.87	3.86
19	20	F	1.58	2.50	70	28.04	110	115	0.96	108	72	68	65.1	42.7	1.52	1.08	-4	-8	1.31	8	12	11	25	29	20.24	11.01	6.3	4.01
20	22	F	1.56	2.43	67	27.53	103	111	0.93	104	68	72	60.6	50.9	1.19	1.05	12	6	1.26	6	10	15	21	27	19.77	10.6	5.91	4.99
21	23	F	1.54	2.37	69	29.09	108	106	1.02	100	66	76	39.4	56.1	0.70	1.14	-2	0	1.3	4	10	19	23	27	16.7	8.81	6.09	3.91
22	25	F	1.58	2.50	67	26.84	99	103	0.96	116	62	74	50.3	52.5	0.96	1.18	0	-4	1.29	8	8	16	19	18	18.75	9.53	5.98	4.14
23	26	F	1.6	2.56	55	21.48	76	92	0.83	106	60	72	43.9	61.1	0.72	1.28	-6	2	1.19	4	12	7	16	20	16.69	11.02	6.02	4.13
24	20	F	1.56	2.43	71	29.17	106	109	0.97	114	70	78	63.5	56.4	1.13	1.2	-2	4	1.35	8	14	18	20	24	17.87	10.94	6.17	3.91
25	23	F	1.55	2.40	56	23.31	80	98	0.82	104	64	74	42.9	51.8	0.83	1.09	0	-2	1.37	4	12	8	13	17	17.3	11.09	5.55	4
26	22	F	1.53	2.34	70	29.90	104	105	0.99	100	72	68	50.4	49.5	1.02	1.04	-2	-2	1.25	8	8	17	21	25	18.01	9.52	4.87	4.14
27	23	F	1.65	2.72	55	20.20	75	94	0.80	106	66	76	49	52.2	0.94	1.04	-2	-4	1.27	6	12	11	20	20	16.91	11.21	6	3.98
28	21	F	1.52	2.31	60	25.97	86	96	0.90	104	64	72	48.4	51.1	0.95	1.02	6	0	1.15	8	8	13	21	29	19.06	10.07	5.75	4.27
29	24	F	1.66	2.76	73	26.49	107	113	0.95	100	60	82	60.2	50	1.20	1.05	-4	-6	1.04	4	10	12	23	26	19.31	10.49	5.59	4.19
30	25	F	1.58	2.50	75	30.04	111	116	0.96	108	64	74	49.7	53.5	0.93	0.98	2	-2	1.19	6	8	17	19	23	20.98	11.01	6	4.06