Review Article

Polycystic Ovary Syndrome: Crossing the Frontiers in Management

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Abstract

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders in women with a heterogeneous clinico-pathologic spectrum characterised by varying degrees of ovulatory dysfunction and clinical and/ or biochemical features of hyperandrogenism. The etiopathogenesis of PCOS remains controversial with multiple genetic variants and environmental factors interacting together to foster development of the spectrum of clinical features. This article explores the evolving concepts of PCOS, focusing on the role of circadian rhythm and white adipose tissue; the role of precision medicine involving interplay of pharmacogenomics, nutrigenomics, chronotherapy and psychotherapy.

Keywords: Polycystic ovarian syndrome, precision medicine, nutrigenomics, pharmacogenomics, chronotherapy

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Historical aspects

Polycystic Ovarian Syndrome [PCOS] alleles are hypothesised to have developed in Paleolithic period of the Stone Age when environmental stressors led to development of susceptibility alleles for modern metabolic diseases.[1]The earliest descriptions have been found in ancient medical records, as early as the period of Hippocrates [460 BC -377 BC] when he observed women with a 'masculine appearance', suffering from scanty periods and infertility.[2]Soranus of Ephesus [98 -138 AD] also mentioned women with 'mannish' appearance, 'sterility' and absent periods.[3]Similar observations have been recorded by Maimonides [1135-1204],[4] Pare [1510-1590 AD].[5]

Human history is replete with instances where women became famous on account of growing a full beard. It is speculated that when Achard [1860-1944] and Theirs [1885-1960], described a condition as 'diabete des femmes a barbe' in 1921 [translation: diabetes of the bearded women], they must have been describing PCOS.[6]

Vallisneri, an Italian physician, in 1721, described the existence of shiny, white, enlarged ovaries in a woman suffering from infertility.[7]This was probably one of the first scientific descriptions of PCOS. However, it was Stein and Leventhal who are credited with first recognition and description of PCOS as a specific syndrome in itself.[8]

Epidemiology

PCOS has a heterogeneous clinico-pathologic spectrum characterised by varying degrees of ovulatory dysfunction and clinical and/ or

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biochemical features of hyperandrogenism. It is recognised as one of the most common endocrine disorders in women, with a prevalence of around 6-10%. The type of phenotypic definition affects the prevalence statistics, varying from 6%; National Institutes of Health [NIH] to 10%; Rotterdam criteria, Androgen Excess and PCOS (AE-PCOS) Society criteria. The prevalence may rise to 20-40% with a first-degree family history of PCOS. The definition of PCOS has generated a lot of controversies and debate in the past. There has been a lot of debate regarding achieving a consensus with definition of PCOS. With an aim of achieving consensus in this regard, an independent panel reviewed the available evidence in 2012 and recommended that Rotterdam criteria be adopted, also mentioning the specific phenotype category[9] (see Table 1).

Etiopathogenesis: Current Perspective

The etiopathogenesis of PCOS has been under immense discussion and research. It is considered a complex genetic trait where multiple genetic variants and environmental factors interact to foster development of the disorder. Genetic targets implicated in the pathogenesis include genes regulating gonadotropin secretion and action, ovarian folliculogenesis, genes involved in insulin metabolism, androgen biosynthesis and function as well as those responsible for weight and energy regulation in humans. The mode of inheritance remains elusive, with the general acceptance of PCOS being a complex trait with several genes interacting with environmental factors to provoke development of a particular phenotype.[10] The fact that PCOS and T2DM share similar genetic susceptibility factors suggest that similar genes may be implicated in pathogenesis.[11] For instance, CAPN10 gene on 2q chromosome is associated with T2DM and has been known to confer PCOS susceptibility in patients.[12]

Genome-wide association studies [GWAS] have been conducted in an attempt to identify putative gene targets. Most of the genes found in proximity of implicated loci are related to control of hormone production and action, insulin resistance and organ growth. However, GWAS identifies loci, not genes, and the pathophysiologic and clinical relevance of the identified loci still needs confirmation. Two loci on chromosome 2 and a third on chromosome 9 have been found to be significantly associated with PCOS. 2p16.3 contains gene for LH/hCG receptor [LHCGR] and 2p21 and 9p33.3 contain multiple single nucleotide polymorphisms [SNPs] independently associated with PCOS. 2p21 locus contains SNPs in THADA, whose gene variant is associated with impaired beta cell function. Loci of interest have been identified near the DENND1A gene, a gene considered to play a role in the hyperandrogenemia of PCOS.

The Concept of Circadian Rhythm

Circadian rhythms are daily cycles of endogenously driven biochemical, physiological and behavioural processes generated by an organism, that oscillate in a 24-hour cycle and can be modulated by cues such as light, temperature, food intake, etc.[13] Their relevance in causation of human diseases is gaining importance as ongoing research are probing into the association of disturbed circadian clocks with disruption in endocrine and metabolic processes. For instance, altered light exposure, shifted exercise patterns and untimely food intake following extended active periods into the night have been found to be associated with development of sleep syndromes, allergies, cardiovascular diseases, neurological and psychiatric disorders, hormone dependent cancers and metabolic diseases. It is suggested that circadian systems in humans consist of a systematic network of several internal clocks, located in different tissues, and connected to a central clock in the brain, called the supra-chiasmatic nucleus (SCN). SCN maintains alignment of central and peripheral oscillators with the help of endogenous signalling mechanisms such as glucocorticoids, melatonin and direct autonomic innervation.[13]

Core circadian clock genes encode for

protein products interlocked through transcriptional/ translational feedback loops, which are necessary for generation and regulation of circadian rhythms. The two major transcriptional activators are CLOCK (Circadian Locomotor Output Cycles Kaput] and BMAL1 [Brain-Muscle-Aryl hydrocarbon receptor nuclear translocator-like protein1). The heterodimeric complex CLOCK:BMAL1 is capable of binding to several thousand sites across the genome in a timely manner.[14] PERIOD [PER1,PER2,PER3] and CRYPTOCHROME [CRY1, CRY2] genes are essential components of a regulatory region. The PER and CRY proteins accumulate in the cytosol, undergo post translational modification and translocate to the nucleus. They auto repress their transcription by binding to and inhibiting CLOCK/BMAL1.After a given period, governed by the circadian rhythm, the PER/CRY heterodimeric repressor complex is degraded and CLOCK/BMAL1 is released and reassumes its transcriptional cycle.[15]

Circadian Rhythm and White Adipose Tissue [WAT]

Excessive fat accumulation is the result of hypertrophy and hyperplasia of white adipocytes in WAT or other organs, due to positive energy balance. This is controlled by a complex circuitry of orexigenic and anorexigenic signals and by a hypothalamus regulated endogenic clock that sets a circadian rhythm of appetite and satiety. WAT is an active endocrine organ that synthesises several biochemical products such as adipokines, cytokines etc., which are known mediators of inflammation. The modern scientific concept is that obesity results from a combination of genomics, metabolomics, endocrine, inflammatory and circadian dysfunctions and behavioural attributes that lead to disturbance of circadian rhythm. McFadden et al. observed 100,000 women and noted increased obesity rates associated with increased levels of LAN exposure.[16] Burdelak et al. found that nurses and midwives with shift jobs, including night shifts had a higher risk of developing obesity.[17] An interesting feature emerged from studies on genetically modified mice, lending further credence to the hypothesis that obesity and circadian rhythm disruption are strongly related. Grosbellet et al.found that genetic modifications in mice causing obesity and diabetes lead to circadian disruption.[18]

Circadian Rhythm and Human Glucose Metabolism

The central circadian clock regulates the coordination of processes involved in human glucose metabolism like food intake, energy expenditure and whole-body insulin sensitivity. These actions are further fine-tuned by local peripheral clocks, such as the one in gut regulating glucose absorption, the one in muscle, adipose tissue and liver regulating local insulin sensitivity patterns and the local pancreatic clock regulating insulin secretion. The insulin secretion by islet cells and insulin sensitivity in target organs exhibit daily rhythmicity. In the middle of night, there is a surge in growth hormone, followed by a surge in cortisol, both of which increase blood glucose production by liver. Blood glucose levels rise between 4 am and 8 am ('Dawn Phenomenon').[19] The system works as a finely coordinated complex of regulators, working in tandem with each other, driven by the innate circadian rhythm of the cells of the body.

Any misalignment between the individual components of the system with the daily rhythm of sleep-wake behavioural cycle predisposes the human body to development of insulin resistance and adverse cardiometabolic endpoints [higher levels of glucose, insulin, ghrelin, cortisol, catecholamines, blood pressure, etc.[20] Genetic, environmental and behavioural factors such as clock gene mutations, artificial light-dark cycles, disturbed sleep, shift work, altered food habits and social jet lag may contribute to circadian disruption.

Precision Medicine

This is an innovative approach to disease prevention and management, which takes

into account the variabilities of each individual based on his/her genetic make-up and environment. The approach is opposite to a one-size-fits-all approach of traditional medicine. NIH launched the Precision Medicine Initiative to understand the interplay of genetics, environment and lifestyle in order to determine the best approach for risk prediction, disease prevention and management.[21] As a component of the programme, NIH launched a study, titled 'All of Us Research Program', which involves a cohort of at least 1 million participants from around the United States who volunteer in providing genetic data, biological samples and other pertinent information regarding their health. The aim is to utilise data obtained to study a large range of diseases, in order to identify risk predictors, improve diagnostic and treatment strategies. It includes the disciplines of pharmacogenomics, nutrigenomics, chronotherapy and psychotherapy.

Pharmacogenomics

The knowledge that genetic variations affect an individual's response to drugs is increasingly being utilised to determine efficacy and safety of medications and dosage calculation depending on a person's genotype. The study applies knowledge of pharmacology with genomics. For instance, 20% of PCOS patients show clomiphene citrate (CC) resistance during ovulation induction (OI). Overbeek et al. investigated whether polymorphism on FSH receptor [p.N680S, rs6166] has effect on drug response, and found that Ser/Ser variant was significantly associated with CC resistance. They attributed this phenomenon to a faulty feedback mechanism in pituitary, which makes it more difficult for these women to overcome FSH threshold after which follicle maturation starts.[22] Valkenburg et al. presented their findings in ESHRE Congress, demonstrating that Ser/Ser variant of the FSH receptor polymorphism was significantly associated with a decreased chance of OI and pregnancy, when treated with CC.[23]

Metformin

Metformin , an insulin sensitiser, has long been given in PCOS. A recent meta-analysis to analyse metformin in PCOS showed an increase in ovulation, improvement in menstrual cyclicity and reduction in serum levels of androgens.[24] It reduces CYP17 activity by improving insulin sensitivity and suppresses androstenedione production by a direct effect on ovarian theca cells to decrease FSH-stimulated 3 beta hydroxysteroid dehydrogenase, StAR protein, CYP11A1 and aromatase activities in both experimental studies on rats and humans.[25] Recently proven, metformin treatment increases AMPK activity in rat granulosa cells, leading to subsequent reduction of steroid synthesis.[26]Polymorphisms in LKB1 gene and STK11 gene have been found to associated with decreased OI in women with PCOS given Metformin.[27] Shu et al. found high degree of polymorphisms in OCT1, an organic cation transporter, and suggested that this could be relevant for patients of PCOS undergoing OI.[28]

Gambineri et al. noted that a reduced response to Metformin with regards to improvement of lipid profile indices was seen in the presence of one of four reduced-function OCT1 variants (including rs12208357/rs72552763).[29] However, the same was not replicated by other experiments. Pederson et al.[30] and Pau et al.[31]studied the effect of genetic polymorphisms on clinical response to metformin. They found that following polymorphisms do not have significant associations with a differing metformin response: OCT1 (rs12208357 and rs72552763), HNF1A (rs1169288 and rs2464196), MATE1 (rs2289669 and rs2252281), MATE2-K (rs12943590) and ATM (rs11212617).

Melatonin

Melatonin is a 'chronobiotic' hormone secreted from pinealocytes during night, under the influence of SCN in both nocturnal and diurnal mammals. It has a global impact on metabolism, influencing the secretory activity of pancreatic islet cells, glucose metabolism in liver and maintaining insulin sensitivity in target tissues. Reduced level of night-time

melatonin is associated with an increased risk of type 2 DM. Melatonin receptors are expressed on hepatocytes viz melatonin receptor type1 (MT1) and type 2 (MT2). It can increase the activity of AMPK and enhance insulin sensitivity in liver. In pancreatic tissue, MT1 is present in alpha cells and MT2 in beta cells. Pre-clinical studies have brought forward interesting features with respect to role of melatonin in glucose metabolism. Bibak et al. administered melatonin [5,10 or 20mg/Kg] to rat model of diabetes. They found that 6 weeks of melatonin reduced serum glucose and triacylglycerol levels.[32] Similar findings were documented by Hidayat et al., who found that 6 weeks of melatonin administration at 10mg/100mldecreased serum glucose levels in diabetic rats.[33] Research are ongoing, trying to see if the rat model can be replicated in humans. Melatonin therapy is also being investigated for use in patients of PCOS as protection against metabolic syndrome co-morbidities.[34]Trials are being conducted to see if melatonin usage can alter the disease process if applied from initial phases of treatment. There is an important role for Precision Medicine for administration of melatonin. It has been observed that carriers of MT2 receptor variant rs10830963 (the MNTR1B risk allele) may actually have heightened insulin resistance when given melatonin, which may hasten development of T2DM.

Nutrigenomics

Human Genome Project [HGP] brought to light the fact that humans share 99.9% of their genomes and a mere 0.1% of gene sequence bears a difference. It is this 0.1% of genome that is responsible for the distinctive difference between two individuals. The main reason for this genetic variation is single nucleotide polymorphisms [SNPs], which can lead to a change in the encoded proteins and lead to molecular variations in response to nutrients/ food compounds. The hallmark of this biological era that began after HGP, the 'Post-Genomic Era', is the application of 'Omics' sciences as a revolutionary tool for scientific research. These 'omics' can be genomics, proteomics, metabolomics, transcriptomics etc. The discovery of epigenome and epigenetic modifications was another major scientific landmark. It gave birth to the field of 'epigenomics', or the study of epigenetic modifications at molecular level.

The epigenome refers to molecules that modify or mark the genome in a manner that enables a cell to perform a particular function. These epigenetic marks or cellular signatures are heritable and are influenced by genotype, environment, diet, drugs etc. Together, all of them determine an individual's phenotype. Nutrigenomics refers to the use of different disciplines of biochemistry, physiology, nutrition, genomics, metabolomics, transcriptomics and epigenomics to determine gene-nutrient interactions at cellular level, and help customise diet according to an individual's genotype.[35]Transcriptomics studies activated RNA transcripts, factors affecting transcription such as nutrients/ bioactive food compounds or their metabolites, hormones etc. Obesity and PCOS are intricately linked to each other. We have ample evidence that both genetic and environmental factors determine the difference in body mass index (BMI) of individuals.

Infact, studies have shown that upto 80% of the differences in BMI of twins are related to genetic factors.The role of nutrigenomics is especially promising in this regards because it gives us a clue regarding the way one's dietary habits interferes with, or facilitates the genetic code, and how the body responds to these interferences. This has led to the emergence of the concept of customised nutritional counselling. Studying the factors which act as sensors to modulate the process of cellular transcription can provide information about the underlying effects of a particular nutrient or diet and help in identifying genes, proteins or metabolites that change in pre-diseases.

There are multiple ways by which food can exert an influence on the expression of genes. One of the primary mechanisms of action is by antagonism of inflammatory mediators

generated during the process of transcription. For instance, interleukin-1[IL-1],[36]a by-product of cellular metabolism, has a key role in many chronic illnesses including obesity. It also stimulates production of many other molecules in the inflammation cascade. Levels of IL-1 are decreased by alpha tocoferol, a bioactive compound found in green tea. There are many studies documenting presence of anti-inflammatory bioactives in some foods, such as caffein acid (Yerba mate), tyrosol (olive oil), quercetin (fruits and green vegetables) and lycopene (tomatoes, guavas and watermelon). These molecules inhibit the expression of COX2 and iNOS genes by reducing the translocation of Kappa B nuclear factor from cytoplasm to nucleus.[37]

The long chain [LC] n-3 PUFA [polyunsaturated fatty acids] EPA [eicosapentaenoic acid] and DHA [docosahexaenoic acid] are potent biological regulators attributed with beneficial roles in cognitive development, learning, vision, immunological response, neurological degeneration and cancer. PCOS is associated with many metabolic aberrations where a positive effect of n-3 PUFA has been demonstrated, for instance abdominal adiposity, chronic inflammation, and post prandial hyperglycemia. Kasim-Karakas et al found an improvement in lipid profile of women treated with a diet enriched with walnuts. Walnuts are a rich source of n-3 PUFA alpha linolenic acid and n-6 linoleic acid.[37]

Cussons et al. administered to the study group; 4g LC n-3 (2.24gm DHA + 1.08gm EPA) for 8 weeks followed by 8 weeks washout period, then treatment with 4gm olive oil (67% oleic acid). They found significant improvement in lipid profiles and liver fat of the subjects.[38] Connor et al. have suggested on the preliminary results of a trial, that diet supplementation with LC n-3 PUFA in women with PCOS has an anti-androgenic effect, which appears to be mediated by a decrease in the plasma n-6:n-3 ratio.[39]

Chronotherapy

It is the study of drug effect with respect to change in biological timing, in order to achieve desired effectiveness of a therapeutic measure [chrono- effectiveness] with minimal toxicity (chronotoxicity).[40] The treatment is thereafter based on body's indigenous timekeeping rhythms of circadian clock. Increasingly being recognised, the biological processes that influence distribution, uptake/efflux and breakdown of a given therapy and elimination of by-products are periodic and most of the rate limiting steps are clock controlled. It is no surprise that drugs will have different effects at different times of the day, given that most of the functions of the human body vary according to the time-of-day with unexpected changes observed during disease states. For instance, the cardiovascular functions, e.g., heart rate, blood pressure, show a 24-hour variation, with cardiovascular emergencies (cardiac arrhythmia, acute myocardial infarction, strokes etc.) exhibiting a clear diurnal variation.[41] Another observation that is gathering evidence is the tendency of shift workers towards type 2 diabetes [T2DM], obesity, cardiovascular disease and increased mortality.[42]

Chronotherapy is a specific field of study wherein 'time-of-day' is a critical variable in deciding 'when' a given treatment modality needs to be administered. The aim is to time the drug availability with the rhythms of the disease, thus optimising therapeutic outcomes while minimising adverse effects. It also encompasses many non-pharmacological strategies that seek to deliver a controlled exposure to environmental stimuli, with an aim to restore the misalignments of the SCN-master clock and peripheral clocks to adjust circadian homeostasis at systems level.

Timed bright light exposure (BLE) is one of the most commonly used non-pharmacological chronotherapeutic measure.It is based on the evidence that light can prompt hormonal regulation especially distribution of pineal hormone melatonin through a non-visual photic input arising from special ganglion cells in the retina, ipRGCs to the SCN. Light suppresses segregation of melatonin, thus

changes the melatonin driven sleep/wake rhythm in mammals. The most commonly recommended approach is a broad-spectrum bright light of 2000 -10,000 lux early morning [6:00am to 8:00am] for 1-3 hours. Chronotherapy gives a new schedule of early waking and early sleeping,and takes some days to adjust. It has the advantage of being drug free and seeks to restore the circadian cycle by changes in the behavioural patterns. It needs a lot of commitment from both the service provider and the patient.

The stressors of the so-called contemporary '24/7' societies have deep seated implications on the metabolism resulting in disruption of circadian clock. Besides, women working in areas involving irregular time schedules and forced exposure to bright LAN [light at night] show significant disruptions in wake-sleep architecture and increased prevalence of insulin resistance, obesity, PCOS etc. Insulin resistance and metabolic disturbance is one of the key features of PCOS. Data is emerging regarding role of chronotherapy in human glucose metabolism. There is need to research into the role of time-of-day therapy in treatment of PCOS. As our internal clocks are linked to blood glucose levels, eating higher carbohydrate meals at midday rather than at night will have a less effect on blood glucose.[43]

Psychotherapy

Prior studies have suggested that PCOS is associated with a higher incidence of mood and psychiatric disorders. Most of the authors have concentrated o depression and anxiety, however, it has been seen that the incidence of bipolar disorder and obsessivecompulsive disorder (OCD) is also higher in women with PCOS.[44] Hirsutism and obesity are two main reasons behind low self-esteem and poor body image, and are associated with considerable psychological distress. Women with a lower BMI have been found to have lower anxiety and depression scores. Data reveals depression to be three times, and anxiety to be four times higher than mean for the general population.[45] Stress may play an important role in derangement of circadian rhythm and persistence of PCOS.[46]This accentuates the importance of early screening, treatment, and monitoring of these women. Further, we also need to research the role of mental stress in etiopathogenesis of PCOS.

Key Message: Role of Newer Modalities in Treatment of PCOS

As the genetics of PCOS is unfolding and the mechanisms becoming clearer, the

Table 1: Specification of Phenotype[47]

Phenotype	Characteristics	Criteria Endorsed by Society		
Phenotype A [Classic PCOS]	Clinical and/or biochemical evidence of hyperandrogenism Oligo-anovulation Polycystic Ovary on Ultrasound	NIH Criteria	AE-PCOS society criteria	Rotterdam Criteria
Phenotype B [Hyperandrogenic anovulation]	Clinical and/or biochemical evidence of hyperandrogenism Oligo-anovulation			
Phenotype C [Ovulatory PCOS]	Clinical and/or biochemical evidence of hyperandrogenism Polycystic Ovary on Ultrasound			
Phenotype D [Non hyperandrogenic PCOS]	Oligo-anovulation Polycystic Ovary on Ultrasound			
**The diagnostic criteria require exclusion of other causes of hyperandrogenism and anovulation				

Table 2: Suggested Socio-behavioral Measures for PCOS Based on Chronobiology

Weight Reduction	
	• Optimisation of BMI to the recommended levels as determined by race
Exercise	
	• Regular exercise including a mixture of weight bearing, non weight bearing and cardio exercises
Dietary Modification	
	• Supplementation with n-3 PUFA
	• Diets rich in carbohydrate should be limited to the first half of day only.
	• Appropriate and regular timing of food intake to be ensured.
	• Intake of a diet rich in antioxidants such as fruits and vegetables
Correction of Sleep wake cycle	
	• Activity to be restricted to daytime
	• Appropriate hours of sleep to be ensured.
	• Avoid LAN [television, computer screens, mobile phones, tablets etc]
Decreasing Stress Levels	
	• Meditation, listening to soothing music, taking relaxing baths etc
Medication	
	• Shift workers and other patients who perceive lack of normal sleep patterns can use light therapy and melatonin supplementation at bedtime to align their circadian rhythm with the rhythm of their lifestyle.
	• A combination of melatonin and metformin can be tried in women with obesity in order to improve insulin resistance along with correction of circadian rhythm.

management is undergoing radical changes. The role of Precision Medicine is emerging as probably highly significant in planning the treatment protocol. What is definitely clear is that a holistic approach is needed, with especial emphasis on correcting the imbalances in circadian rhythm of an individual. It is extremely important to raise awareness amongst general population, patients as well as specialists treating the patients, on the importance of appropriate timing for food intake, daytime activity, exposure to sunlight and proper sleep. However, we still have a long way to go in order to be able to synchronise all the information of PCOS with genetic profile of individuals, dietary habits and environmental habits. Until we are able to identify the key players in the mechanism that triggers development of PCOS, we can probably issue tentative advice to patients, (see Table 2) based on pre-clinical and preliminary clinical data.

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References

1. Blekhman R, Man O, Herrmann L, Boyko AR, Indap A, Kosiol C, et al. Natural selection on genes that underlie human disease susceptibility. Curr Biol. 2008;18:883-9.
2. Hanson AE. Hippocrates: Diseases of Women 1. Signs (Chic). 1975;1:567-84.
3. Temkin, O. Soranus' Gynecology. Baltimore, USA: Johns Hopkins University Press; 1991.
4. Rosner F, MunterS. The medical aphorism of moses maimonides, Vol. II. New York, USA: Yeshiva University Press; 1971.
5. Azziz R, Dumesic DA, Goodarzi MO. Polycystic Ovary Syndrome: An Ancient Disorder. Fertil Steril. 2011;95(5):1544-48
6. de Herder WW. Cllementing dealt (1865-1934), the most famous bearded lady on the continent in the 20th century. Gynecol Endocrinol. 2020;36(3):213-7
7. Vallisneri A, 1721. Cited in Insler V, Lunesfeld B. Polycystic ovarian disease: A challenge and controversy. Gynecol Endocrinol. 1990;4:51-69.
8. Stein IF, Leventhal NL. Amenorrhea associated with bilateral polycystic ovaries. Am J Obstet Gynecol. 1935;29:181.
9. Johnson T, Kaplan L, Ouyang P, Rizza R. National Institutes of Health evidence-based methodology workshop on polycystic ovary syndrome (PCOS). NIH EbMW Report. 2013.Bethesda, MD, USA: National Institutes of Health; 2013. p.1–14.
10. Crosignani PG, Nicolosi AE Polycystic ovarian disease: heritability and heterogeneity. Hum Reprod Update. 2001;7:3-7.
11. Gonzalez A, Abril E, Roca A, Aragon MJ, Figueroa MJ, Velarde P, et al. Specific CAPN10 Gene Haplotypes Influence the Clinical Profile of Polycystic Ovary Patients. J Clin Endocrinol Metab. 2003;88(11):5529-36.
12. Gonzalez A, Abril E, Roca A, Aragon MJ, Figueroa MJ, Velarde P, et al.CAPN10 alleles are associated with polycystic ovary syndrome. J Clin Endocrinol Metab. 2002;87:3971-6.
13. Selfridge JM, Gotoh T, Schiffhauer S, Liu J, Stauffer PE, Li A, et al. Chronotherapy: intuitive, sound, founded…but not broadly applied. Drugs. 2016;76(16):1507-1521.
14. Lowrey PL, Takahashi JS. Genetics of circadian rhythms in Mammalian model organisms. Adv Genet. 2011;74:175-230.
15. Lee C, Etchegaray JP, Cagampang FR, Loudon AS, Reppert SM. Posttranslational mechanisms regulate the mammalian circadian clock. Cell. 2001;107(7):855–67.
16. McFadden E, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ. The relationship between obesity and exposure to light at night: cross-sectional analyses of over 100,000 women in the Breakthrough Generations Study. Am J Epidemiol. 2014;180(3):245-50.
17. Burdelak W, Peplonska B. Night work and health of nurses and midwives – a review [Article in Polish] [Abstract]. Med Pr. 2013;64:397-418.
18. Grosbellet E, Dumont S, Schuster-Klein C, Guardiola-Lemaitre B, Pevet P, Criscuolo F, Challet E. Circadian phenotyping of obese and diabetic db/db mice. Biochimie. 2016;124:198-206.
19. Diabetes Self-Management. Circadian Rhythm. Available from: https://www. diabetes self management.com/diabetes-resources/definitions/ circadian-rhythm/ [Accessed on 10th July, 2020]
20. Scheer FA, Hilton MF. Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Natl Acad Sci. 2009;106:4453-58.
21. National Library of Medicine (NLM). What is the Precision Medicine Initiative? Available from: https://ghr.nlm.nih.gov/primer/precisionmedicine/ initiative [Accessed on 10th July, 2020].
22. Overbeek A, Kuijper EA, Hendriks ML, Blankenstein MA, Ketel IJ, Twisk JW, et al. Clomiphene citrate resistance in relation to follicle-stimulating hormone receptor Ser680Ser-polymorphism in polycystic ovary syndrome. Hum Reprod. 2009;24(8):2007-13.
23. Valkenburg O, van Santbrink EJ, König TE, Themmen AP, Uitterlinden AG, Fauser BC, et al. Follicle-stimulating hormone receptor polymorphism affects the outcome of ovulation induction in normogonadotropic (World Health Organization class 2) anovulatory subfertility. Fertil Steril. 2015;103(4):1081-1088.e3.
24. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev. 2010:CD003053.
25. Palomba S, Falbo A, Zullo F, Orio F. Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: a comprehensive review. Endocr Rev.2009;30:1-50.
26. Tosca L, Solnais P, Ferre P, Foufelle F, Dupont J. Metformin-induced stimulation of adenosine 5′ monophosphate-activated protein kinase (PRKA) impairs progesterone secretion in rat granulosa cells. Biol Reprod. 2006;75:342-51.
27. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. Ovulatory response to treatment of polycystic ovary syndrome is associated with a polymorphism in the STK11 gene. J Clin

Endocrinol Metab. 2008;93:792-800.
28. Shu Y, Brown C, Castro RA, Shi RJ, Lin ET, Owen RP, et al. Effect of genetic variation in the organic cation transporter 1, OCT1, on metformin pharmacokinetics. Clin Pharmacol Ther. 2008;83(2):273-80.
29. Gambineri A, Tomassoni F, Gasparini DI, Di Rocco A, Mantovani V, Pagotto U, et al. Organic cation transporter 1 polymorphisms predict the metabolic response to metformin in women with the polycystic ovary syndrome. J Clin Endocrinol Metab. 2010;95: E204-8.
30. Pedersen AJT, Stage TB, Glintborg D, Andersen M, Christensen MMH. The pharmacogenetics of metformin in women with polycystic ovary syndrome: a randomised trial. BasicClinPharmacol Toxicol. 2018;122:239-44.
31. Pau CT, Cheang KI, Modi BP, Kasippillai T, Keefe CC, Shulleeta M, et al. The role of variants regulating metformin transport and action in women with polycystic ovary syndrome. Pharmacogenomics 2016;17:1765-73.
32. Bibak B, Khalili M, Rajaei Z, Soukhtanloo M, Hadjzadeh MA, Hayatdavoudi P. Effects of melatonin on biochemical factors and food and water consumption in diabetic rats. Adv Biomed Res. 2014;3:173.
33. Hidayat M, Maha Y, Wasim H.Effect of melatonin on serum glucose and body weight in streptozotocin induced diabetes in albino rats. J Ayub Med Coll. 2015; 27:274-6.
34. Spinedi EJ, Cardinali DP. The Polycystic ovary syndrome and the metabolic syndrome: a possible chronobiotic-cytoprotective adjuvant therapy. Int J Endocrinol. 2018;6:1-12.
35. Sales NMR, Pelegrini PB, Goersch M C. Nutrigenomics: definitions and advances of this new science. J Nutr Metab. 2014;1-6.
36. Cozzolino SMF, Cominetti C. Biochemical and physiological bases of nutrition in different stages of life in health and disease. 1st ed. Monole, Sa˜o Paulo, Brazil: 2013.
37. Dalmiel L, VargasT, Molina AR. Nutritional genomics for the characterization of the effect of bioactive molecules in lipid metabolism and related pathways. Electrophoresis J. 2012;33(15):2266–89.
38. Cussons AJ, Watts GF, Mori TA, Stuckey BG. Omega-3 fatty acid supplementation decreases liver fat content in polycystic ovary syndrome: a randomized controlled trial employing proton magnetic resonance spectroscopy. J Clin Endocrinol Metab. 2009;94(10):3842-8.
39. Connor AO, Ginny J, Roche HM. Metabolic and hormonal aspects of polycystic ovary syndrome: the impact of diet. Proc NutrSoc. 2010;69:6286-35.
40. Reinber AE. Concepts in chronopharmacology. Annu Rev Pharmacol Toxicol. 1992;32:51-66.
41. Pandit V, Suresh. Emerging role of biorhythms in optimising treatment of disease. Indian J novel drug delivery. 2009;1:2-10.
42. Karlsson B, Knutsson A, Lindahl B. Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27,485 people. Occup Environ Med 2001;58:747-52.
43. Jough SS, Singh SP, Singh Y, Gupta D, Saxena P, Gypta S, Singh A, Srivastva A. Chronopharmacology: Recent Advancemenst in the Treatment of Diabetes Mellitus through Chronotherapy. IJPPR. Human. 2017;9(2):87-9.
44. Brutocao C, Zaiem F, Alsawas M, Morrow S, Murad MH, Javed A. Psychiatric Disorders in Women With Polycystic Ovary Syndrome- A Systematic Review and Meta-analysis. Endocrine 2018;62(2):318-25.
45. Cooney LG, Lee I, Sammel MD, Dokras A. High prevalence of moderate and severe depressive and anxiety symptoms in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod. 2017;32(5):1075-1091.
46. Damone AL, Joham AE, Loxton D, Earnest A, Teede HJ, Moran LJ. Depression, Anxiety and Perceived Stress in Women With and Without PCOS: A Community -Based Study. Psychol Med. 2019;49(9):1510-20.
47. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, Piltonen T, Norman RJ; International PCOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil Steril. 2018;110(3):364-79.