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LABORATORY DIAGNOSTIC LINK TO POLYCYSTIC OVARY SYNDROME – AN UPDATE

Rajeswari S[1], Gowri Meena S[2] and Swaminathan S[3*]

[1]Junior Technical Officer, Department of Biochemistry, Apollo Speciality Hospitals, Vanagaram and Research Scholar, Department of Biochemistry, Vels University, Chennai, 600117.
[2]Consultant, Department of Obstetrics & Gynaecology, Apollo Speciality Hospitals, Vanagaram.
[3]Senior Consultant and Head, Department of Biochemistry, Apollo Speciality Hospitals, Vanagaram.

***Author for Correspondence: Swaminathan S.**
Senior Consultant and Head, Department of Biochemistry, Apollo Speciality Hospitals, Vanagaram.

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ABSTRACT
Polycystic ovary syndrome (PCOS) is a common endocrine disorder among women of reproductive age, occurring in approximately among 15% of women in India and it is the leading cause of infertility. Hormonal imbalance has been identified as the leading cause for PCOS. Calcium, Magnesium & Vitamin D deficiencies along with insulin resistance have been implicated as causes of PCOS and their supplementation has been highlighted in many studies. Weight loss management improves follicle maturation, menstrual regularity and improvement of hyperandrogenism. The high prevalence of 25(OH)D deficiency in PCOS is a common findings and is a real alarm for public health care system. Women with PCOS had the highest odds of diabetes and an increased risk of cardiovascular disease. Hyperprolactinemia is also frequently reported in PCOS. The rate of patients with elevated LH levels and LH/FSH ratio were significantly higher in the late phase than in the early phase among PCOS. This review article present the research findings related to laboratory diagnosis with special emphasis on the role of calcium, Vitamin D, magnesium, prolactin, LH and FSH.

KEYWORDS: PCOS, Calcium, Vitamin D, LH, FSH.

INTRODUCTION
PCOS is a common heterogeneous endocrine disorder characterized by irregular menses, hyperandrogenism and polycystic ovaries. Women with PCOS are more likely to have increased coronary artery calcium scores and increased carotid intima-media thickness. Mental health disorders including depression, anxiety, bipolar disorder and binge eating disorder also occur more frequently in women with PCOS. Weight loss improves menstrual irregularities, symptoms of androgen excess, and infertility. Management of clinical manifestations of PCOS includes oral contraceptives for menstrual irregularities and hirsutism. Spironolactone and finasteride are used to treat symptoms of androgen excess. Treatment options for infertility include clomiphene, laparoscopic ovarian drilling, gonadotropins and assisted reproductive technology.

PCOS and Vitamin D/ Calcium (Ca)
Recent data suggest that metformin may play an important role in ovulation induction in diabetic patients with PCOS. Proper diagnosis and management of PCOS is essential to address patient concerns but also to prevent future metabolic, endocrine, psychiatric and cardiovascular complications.[1] 83% of all PCOS patients showed vitamin D deficiency while 35% were severely deficient and serum 25-OH-vitamin D (Vitamin D) mean levels were 13.38 ± 6.48 ng/mL. Vitamin D deficiency was recompensed in 74% of the PCOS patients who had taken calcium & vitamin D supplementation. There was no correlation between Body Mass Index (BMI) and Vitamin D before and after the treatment, confirming that the positive effects of Ca & vitamin D supplementation on weight loss, follicle maturation, menstrual regularity and improvement of hyperandrogenism in infertile women with PCOS.[2] Vitamin D repletion with Ca therapy resulted in normalized menstrual cycles within 2 months with resolution of their dysfunctional bleeding. These observations suggest that abnormalities in Ca homeostasis may be responsible, in part, for the arrested follicular development in women with PCOS and may contribute to the pathogenesis of PCOS.[3] Ca and Vitamin D levels had no significant differences in patients with overweight and Insulin Resistance (IR), but a relationship between Vitamin D level and metabolic syndrome (MS) was found. There was a correlation between Vitamin D and BMI in control group, while the C-reactive protein (CRP) level was predominantly higher in PCOS group. Although the difference of Vitamin D

level between PCOS and healthy women is not significant, the high prevalence of Vitamin D deficiency in PCOS is a real alarm for public health care system.[4]

Androgen and Blood Pressure (BP) profiles improved after three months intervention by supplementing with Vitamin D & Calcium, suggesting therapeutic implications in overweight and vitamin D deficient women with PCOS.[5] PCOS women within the highest quartile of Ca intake had significantly lower testosterone and androstenedione and significantly higher high-density lipoprotein (HDL) levels than PCOS women with lower Ca intake. Results indicate an association of Adult Type Hypolactasia (ATH) with PCOS susceptibility. Moreover, ATH might influence waist-to-hip ratio, HbA1c and fasting glucose scores as well as Vitamin D levels. Higher Ca intake was associated with lower androgens and higher HDL levels.[6] The frequency of hirsutism and acne were not different among groups viz Metaformin, Metaformin, Ca and Vitamin D, Ca and vitamin D and Placebo and the frequency of regular menstrual cycle and dominant follicle were significantly higher. After trial, there was no significant difference with respect to BMI. Vitamin D and Ca supplementation in addition to metformin therapy in women with PCOS could result in a better outcome in a variety of PCOS symptoms including menstrual regularity and ovulation.[7]

No differences were found in the absolute level of serum vitamin D between PCOS patients and matched controls. Prevalence of vitamin D deficiency was equally common among both patients and controls. No correlations was found between serum vitamin D level and clinical or metabolic profiles, suggesting that the role of vitamin D in the pathogenesis of PCOS is not yet clear.[8] Ca plus vitamin D cosupplementation for 8 weeks among overweight and vitamin D-deficient women with PCOS had beneficial effects on inflammatory factors and biomarkers of oxidative stress.[9]

Lipid peroxidation levels were higher in the PCOS group than those in the control although neutrophil glutathione peroxidase (GSH-Px) and reduced glutathione (GSH) values were decreased. Selenium appeared to provide a protective effect against oxidative stress and Ca ions entry through modulation of neutrophil TRPV1 Ca channels.[10] The association of hypoadiponectinemia and PCOS was not significant considering Vitamin D as a confounding factor. A study indicates that the association of hypoadiponectinemia with PCOS is dependent on vitamin D, suggesting a beneficiary effect of vitamin D on the metabolic parameters in PCOS.[11] A significant decrease in serum triglycerides and VLDL-cholesterol levels was seen following the administration of Ca plus vitamin D supplements compared with the control group. Co-supplementation with Ca and vitamin D had no significant effects on fasting Plasma Glucose (FPG), total-, LDL-, HDL-, and non-HDL-cholesterol levels. Ca plus vitamin D supplementation for eight weeks among vitamin D deficient women with PCOS had beneficial effects on serum insulin levels, HOMA-IR, quantitative insulin sensitivity check index, serum triglycerides and VLDL-cholesterol levels, but it did not affect FPG and other lipid profiles.[12]

PCOS and Magnesium (Mg)

Mg deficiency is not associated with IR in PCOS. As per a study, serum Ca level is more potent predictor of PCOS than serum Mg and only Ca, not Mg, is related to IR in PCOS.[13] Significantly lower serum Mg ions and total Mg and a significantly higher serum Ca/Mg ratio has been observed in PCOS patients compared with the controls. No correlation was found, however, between the serum concentrations of steroid hormones (estrogen, progesterone and testosterone), or any of the cations in the PCOS patients or the controls.[14] Mg levels do not correspond with age, BMI, waist circumference, insulin sensitivity, glycemic levels, blood pressure or lipid levels in reproductive-age women with PCOS. Mg concentrations are similar across PCOS phenotypes and indistinguishable from women without PCOS.[15] Antioxidants and vitamins have positive effects on management of PCOS women.[16] The first phase of insulin secretion was significantly increased after treatment with alphacalcidol. A favorable statistically significant change also was observed in the lipid profile.[17]

Low serum Vitamin D concentrations result from the presence of obesity and IR. However, the dependency between PCOS and hypovitaminosis D is questionable. Hypovitaminosis D should be kept in mind while managing obese women with PCOS.[18] Vitamin D deficiency is common in women with PCOS, with 67-85% of women with PCOS having serum concentrations of Vitamin D <20 ng/mL. Vitamin D deficiency may exacerbate symptoms of PCOS, with observational studies showing lower Vitamin D levels associated with IR, ovulatory and menstrual irregularities, lower pregnancy success, hirsutism, hyperandrogenism, obesity and elevated cardiovascular disease risk factors. Vitamin D deficiency may play a role in exacerbating PCOS, and there may be a place for vitamin D supplementation in the management of this syndrome, but current evidence is limited and additional randomized controlled trials are required to confirm the potential benefits of vitamin D supplementation in this population.[19] Current evidence suggests an inverse association between vitamin D status and metabolic disturbances in PCOS. Owing to the heterogeneity of the studies, it is hard to draw a definite conclusion. The causal relationship between vitamin D status and metabolic disturbances in PCOS remains to be determined in well-designed placebo-controlled randomized clinical trials.[20] Additional randomized trials are required to establish the correct dose of vitamin D and to confirm the effectiveness of vitamin D treatment in PCOS disorders. However; it seems evident that correct supplementation of vitamin D is beneficial in the management of women with PCOS and low Vitamin

D serum levels, and that it could be helpful in improving the effects of PCOS treatment.[21]

Multiple regression analysis established the role of vitamin D as the best predictor of IR. Vitamin D has an important role in the pathogenesis of IR in PCOS.[22] Vitamin D deficiency is highly prevalent in PCOS women in Scotland, and a larger proportion of PCOS patients than control women were found to be vitamin D deficient. It is also observed that correlations of vitamin D status with insulin sensitivity, HDL-C and CRP in PCOS patients support the increasing evidence that vitamin D deficiency is associated with multiple metabolic risk factors in PCOS women.[23] There was no association of Vitamin D deficiency with gonadotropins and sex hormones except sex hormone binding globulin (SHBG). IR as a better independent risk factor for the presence of vitamin D deficiency than SHBG. The IR and vitamin D deficiency significantly predicted the obesity risk in PCOS women.[24] PCOS women with MS had lower serum Vitamin D compared with those without MS. Vitamin D correlated positively with HDL cholesterol in all subjects and negatively with luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio. IR and other metabolic abnormalities seems to be related to women with PCOS rather than to vitamin D deficiency alone.[25]

A study was unable to demonstrate the effect of vitamin D supplementation on insulin sensitivity and IR in women with PCOS and vitamin D deficiency.[26] Vitamin D was also favorably associated with primary dysmenorrhea, uterine leiomyoma and ovarian reserve in late reproductive aged women. In women undergoing in-vitro fertilization, a sufficient vitamin D level (≥30ng/mL) should be maintained. Vitamin D supplementation will improve metabolic parameters in women with PCOS. A high vitamin D intake might be protective against endometriosis.[27] In women with PCOS, insulin sensitivity was unchanged with high-dose vitamin D, but there was a trend toward decreased 2-hour insulin and a protective effect on BP.[28] vitamin D might influence steroidogenesis of sex hormones (estradiol and progesterone) in healthy women and high Vitamin D levels might be associated with endometriosis. In men, vitamin D is positively associated with semen quality and androgen status. Moreover, vitamin D treatment might increase testosterone levels. Testiculopathic men show low CYP21R expression, low Vitamin D levels, and osteoporosis despite normal testosterone levels.[29]

The effects of metformin and Ca/ Vitamin D in regulating the menstrual cycle suggest that they could also be effective for the treatment of anovulation and oligomenorrhea, with possible consequences for pregnancy rates in PCOS patients.[30] Confirmation of experimental observations establishing an association of vitamin D deficiency with adverse reproductive outcomes by high quality observational and large-scale randomized clinical trials is still lacking. The determination of optimal Vitamin D levels in the reproductive period and the amount of vitamin D supplementation required to achieve those levels for the numerous actions of vitamin D throughout a woman's life would have important public health implications.[31] Majority of the patients and controls had vitamin D deficiency and there was no difference in the vitamin D levels in PCOS group and controls as well as obese and non obese groups.[32] Approximately two-thirds will not ovulate on a regular basis and consequently may therefore seek treatment for ovulation induction. Women with PCOS are potentially at an increased risk of miscarriage and in pregnancy they are at an increased risk of developing gestational diabetes (GD), pregnancy-induced hypertension and pre-eclampsia. Furthermore the neonate has a significantly higher risk of admission to a neonatal intensive care unit and a higher perinatal mortality.[33]

In women with PCOS for whom time is of the essence and rapid establishment of pregnancy is desired, clomiphene should be the first-line agent. The addition of metformin to clomiphene has been shown to increase the cumulative ovulation rate, but it remains unclear whether it increases the odds of a live birth. In women with PCOS for whom pregnancy is a goal at a more distant time (>6 months), initial treatment with metformin, combined with diet and exercise, is an option to induce ovulation. An advantage of achieving pregnancy with metformin versus clomiphene in this situation may be a decrease in the risk of multiparity. Infertility treatment needs to be individualized, and these recommendations attempt to take into account the needs and preferences of patients with PCOS, who may differ with respect to the urgency of achieving pregnancy and the willingness to risk multiparity. They also recognize continuing uncertainties in the field that warrant continued investigation.[34] The prevalence of PCOS among ovulatory women with infertility is higher than that in the normal population, suggesting that PCOS may, perhaps by virtue of an effect of hyperandrogenaemia, contribute to the causes of subfertility in women with regular menses.[35] Limited research has been published about the efficacy of oral contraceptives in producing conception. If pregnancy still eludes women with PCOS after initial pharmacologic treatments, gonadotropin therapy by itself or in conjunction with assisted reproductive therapy is considered. These treatments come with higher expense, and increased risk and require extensive counseling prior to implementation. Additional research is needed to better understand what risks exist for pregnant women with PCOS and for their newborns.[36]

Metformin should be considered as first-line therapy because it has the advantage to allow for normal single ovulation, for reduced early pregnancy loss, and, most importantly, lifestyle modifications and weight loss before pregnancy. Losing weight not only improves fertility but also reduces adverse pregnancy outcomes

associated with obesity.[37] Aromatase inhibitors are presently being examined and may replace clomiphene in the future. When all else has failed, IVF/ET produces excellent results. There are very few women suffering from anovulatory infertility associated with PCOS who cannot be successfully treated today.[38] Polycystic ovaries are common among women with infertility, however they are not necessarily associated with PCOS. Doctors should investigate their clients for PCOS and offer appropriate treatment.[39]

PCOS and Diabetes Mellitus (DM)

Hyperinsulinemia associated with IR has been causally linked to all features of the syndrome, such as hyperandrogenism, reproductive disorders, acne, hirsutism and metabolic disturbances. If beta-cell compensatory response declines, relative or absolute insulin insufficiency develops which may lead to glucose intolerance and Type 2 Diabetes Mellitus (T2DM). Moreover, IR in PCOS may be considered a risk factor for GD.[40] The risk of PCOS among reproductive-aged T2DM patients appears to be similarly increased. It remains to be determined whether PCOS and T2DM represent no more than different clinical manifestations of the same IR syndrome, with their phenotypic differences due to the presence or absence of a coincidental genetic defect at the level of the ovary or pancreas, respectively, or representing the result of etiologically different subtypes of IR syndromes.[41] The link between PCOS and T1DM is believed to implicate supraphysiological concentrations of insulin within the systemic circulation. Further progression of the obesity epidemic will ensure even greater prominence of important obesity-related conditions such as PCOS and T2DM. Research to gain a clearer understanding of the mechanisms linking each condition should be a priority.[42]

Correlations between metabolic and reproductive parameters were consistent with a stimulatory action of insulin on the ovary. Women with T2DM have a higher prevalence of polycystic ovaries than that reported in the general population. Not all women with hyperinsulinaemia due to T2DM, however, develop PCOS suggesting that hyperinsulinaemia alone is not sufficient for the expression of this ovarian morphology.[43] There was a significant dependence of babies' birthweight on mother's BMI.[44] There were no significant differences between hyperandrogenic and nonhyperandrogenic in T1DM women in clinical variables such as the duration of diabetes, age at diagnosis of diabetes, conventional or intensive insulin therapy, mean daily insulin dosage, or metabolic control. Women with T1DM have a high prevalence of hyperandrogenic disorders, including PCOS and hirsutism.[45] While PCOS has important metabolic associations, and short-term interventions reduce risk factors for T2DM and CVD, data on prevalence and incidence of T2DM and particularly CVD are poor. There is a need for a clear definition of PCOS, for diabetes screening protocols and for long-term studies to determine whether risks can be reduced.[46]

Normal-weight women with PCOS had a three fold higher odds of incident diabetes compared with normal-weight women without PCOS. Compared with those without PCOS, women with persistent PCOS had the highest odds of diabetes. PCOS is associated with subsequent incident diabetes and dyslipidemia, independent of BMI. Diabetes risk may be greatest for women with persistent PCOS symptoms.[47] In a follow-up study of a relatively lean PCOS population, the prevalence of DM and hypertension was increased when compared with the Dutch female population, especially in women aged 45--54 years.[48] PCOS women are at significantly increased risk for Imparied Glucose Tolerance and T2DM at all weights and at a young age and the these prevalence rates are similar in two different populations of PCOS women, suggesting that PCOS may be a more important risk factor than ethnicity or race for glucose intolerance in young women; and the American Diabetes Association diagnostic criteria failed to detect a significant number of PCOS women with diabetes by postchallenge glucose values.[49]

PCOS and Prolactin (PRL)

Hyperprolactinemia in PCOS is quite common and PCOS is the most frequent cause of female infertility. Both pathologies are characterized in common by several clinical features. PRL concentrations should be assessed in each woman with PCOS suspicion because of certain common clinical signs are observed in both disorders. Every woman diagnosed with PCOS and hyperprolactinemia should further be examined in terms of the actual causes of hyperprolactinemia because the coexistence of these two disease entities is a distinct possibility.[50]

The true prevalence rate of hyperprolactinemia in PCOS may be low rather than high and the association of hyperprolactinemia with PCOS may be coincidental rather than a pathogenically related phenomenon.[51] Multiple regression analysis showed that PRL levels were associated with Mean Platelet Volume (MPV) levels and mean platelet volume levels are significantly increased in women with PCOS having mildly elevated PRL. In women with PCOS, elevated PRL levels may increase the risk of developing atherothrombotic events via the activation of platelets.[52]

Abnormal secretion of PRL was observed in some patients with PCOS, and a statistically significant correlation was found between mean PRL concentrations and the mean plasma dehydroepiandrosterone sulphate (DHEAS) concentration. These data suggest that a significant portion of women with PCOS syndrome have abnormalities of PRL secretion.[53] In the patient population PRL levels were inversely associated with age, smoking status, waist circumference, total cholesterol, triglyceride and LDL and positively

associated with HDL, estradiol, total testosterone, dehydroepiandrosterone sulfate, 17-hydroxyprogesterone and cortisol levels. In multiple regression analyses, PRL was inversely associated with LDL and positively associated with estradiol, 17-hydroxyprogesterone and cortisol after correcting for age, BMI and smoking status in patients with PCOS. The inverse associations between PRL levels and metabolic risk markers are supported by studies in populations of women without PCOS. The association between PRL and adrenal activity should be evaluated in future studies.[54]

Normal PRL increments occur after ovulation and a blunted response follows a period of anovulation, and failure to find a consistent abnormality of lactotroph function in patients with PCOS other than that associated with anovulation.[55] The most distressing aspect of PCOS for any given patient may change over time, from hirsutism as a teenager to infertility as a young adult–potentially requiring several different providers along the way. It is important, therefore, that those caring for these patients understand not only the management issues pertinent to their specialty, but also appreciate the other potential health risks in these women. Recent insights into the pathophysiology of PCOS have shown IR to play a substantial role and as such have brought the long-term issues of T2DM and its resultant increased risk of CVD to the forefront. It is hoped that some clarity in this regard will allow more women to be diagnosed and managed properly for their presenting symptoms (hirsutism, irregular menses, etc.), but also to be educated and managed for the continuing health risk of IR throughout their lives.[56] Mean FPG/insulin and glucose/insulin-AUC ratios were significantly lower in obese PCOS when compared with all other groups. These data support the existence of low hypothalamic dopaminergic activity tone in PCOS women that is likely involved in the inappropriate LH and PRL secretion frequently seen in this syndrome. In addition it is suggested that changes in PRL bioactivity in obese PCOS that may play a role in the development of hyperinsulinemia; however, whether PRL has a functional significance in the development of the metabolic disturbances frequently seen in PCOS remains to be elucidated.[57] Hyperprolactinemia is frequently reported with PCOS. However, there is a controversy whether they share a common mechanism or have cause–result relationship or just are coincidental. In univariate analysis, the serum prolactin levels did not correlate with any of the the following parameters: HOMA-IR score, total testosteron, free testosteron, DHEA-S, LDL-C, HDL-C, triglyceride, LH or FSH. Since hyperprolactinemia is not a clinical manifestation of PCOS, patients with increased PRL levels should be investigated for other causes of hyperprolactinemia.[58]

PCOS and LH, FSH

LH/FSH ratio is not a characteristic attribute of all PCOS women and in a study this abnormality was detected in a sub population smaller than 50%. Most of the PCOS women with normal gonadotropin ratio belong to a group of patients suffering from hyperinsulinemia and obesity. Patients with hyperinsulinemia and excess of LH constitute a selected and distinct sub group with increased adrenal androgenic activity.[59] The LH/FSH ratio is often requested to help diagnose PCOS despite a recent consensus recommending against its use. The median LH/FSH ratio for individual subjects did not differ significantly between the PCOS and the non-affected group. Only 7.6% of samples from PCOS patients had an LH/FSH ratio above three, compared with 15.6% of samples from normal subjects, confirmong that measurement of the LH/FSH ratio is of limited use in the diagnosis of PCOS.[60]

The total number of retrieved oocytes and the number of mature oocytes was also significantly higher in women with LH/FSH ratio > 1.5 than in those with a lower ratio. However, the pregnancy rate in women with LH/FSH ratio of > 1.5 (16.7%) was significantly lower than in those with a ratio of 0.5-1.5 (40.4%), odds ratio 0.32. PCOS patients with LH/FSH ratio > 1.5 had higher basal testosterone, E2, and AFC but decreased pregnancy rate. This could be due to the deleterious effect of LH on folliculogenesis and endometrial receptivity.[61] Testosterone, androstenedione or LH, either alone or in combination, were raised in 86% of women with PCOS and these should be the definitive hormonal tests. Using LH/FSH ratio as a biochemical criterion for diagnosis of PCOS should be abandoned because of its low sensitivity. To be of value the normal range for all hormones should be precisely defined in a group of regularly ovulating women in the early follicular phase of the cycle for the assay used in each laboratory.[62] Age and hysterectomy-adjusted regression models suggest that CRP level is positively associated with LH/FSH ratio and LH/FSH>1, high glucose level and LH/FSH>2 are inversely related and HDL<50mg/dL is positively associated with both LH/FSH>1 and LH/FSH>2. In a nationally representative sample of post-menopausal women, markers of chronic inflammation and dyslipidemia which are characteristics of PCOS-associated morbidities were also significantly associated with LH/FSH ratio, meriting further investigation.[63]

Clinicians should be aware that the use of monoclonal LH assays will result in significantly lower measured LH levels and LH/FSH ratios in women with PCOS than previously used polyclonal assays. Account should be taken of the assay type used, when using endocrinological parameters in the diagnosis of PCOS, or the identification of women who have LH hypersecretion.[64] Both I-LH and B-LH levels were higher in PCOS patients respectively, compared with all phases of the normal cycles except the mid-cycle peak. The LH and FSH levels and the ratio in PCOS patients during suppression were comparable with levels in the early and mid-follicular phases of control cycles but the LH/FSH ratio remained significantly raised.[65] In women

who miscarried, the mean LH/FSH ratio was significantly higher than in women having a live birth. In PCOS patients stimulated with Human Menopausal Gonadotrophin (HMG), a high basal LH/FSH ratio appears to have an adverse effect on the number of follicles and oocytes, as well as on oocyte maturity. On the other hand, the administration of GnRH in the long protocol seems to reverse this detrimental effect on follicle and oocyte development. Furthermore, a higher LH:FSH ratio seems to predict a greater possibility for miscarriage, despite the use of GnRH.[66]

Elevated LH and LH/FSH ratio were significantly higher in the late phase than in the early phase in patients with PCOS. In the early phase, only 52% of patients had elevated LH levels and LH/FSH ratio, which failed to demonstrate an inverse relationship between LH and BMI. LH levels of patients with PCOS were strongly influenced from the onset of menses. In the early period, the reproducibility of elevated LH or LH/FSH ratio was poor even in PCOS patients previously diagnosed.[67] Metformin does indeed modulate the basal level of LH and LH/FSH ratio, albeit indirectly, particularly in patients with PCOS, suggesting that metformin does directly regulate FSH gene expression.[68] Women with PCOS have higher baseline and GnRH-stimulated LH concentrations and GnRH stimulation results in an increase in LH/FSH ratio in women with PCOS, and that this phenomenon might be potentially useful as an additional tool in the diagnosis of PCOS.[69]

Overweight/obese women with PCOS are at an increased risk for sonographic view of polycystic ovaries. Therefore, it is suggested that successful weight loss is the most effective method of restoring ovulation and menstruation that should be used as major advice in obese PCOS patients.[70] As such, women with PCOS require higher levels of progesterone to slow the frequency of GnRH pulse secretion, resulting in inadequate FSH synthesis and persistent LH stimulation of ovarian androgens. The decreased sensitivity of the GnRH pulse generator may help to explain the genesis of PCOS during puberty. In normal early puberty, sleep-entrained increases in LH stimulate ovarian steroids, which subsequently suppress LH frequency and amplitude during the subsequent day. In hyperandrogenemic girls destined to develop PCOS, this nocturnal increase in ovarian steroids may not be adequate to suppress the GnRH pulse generator, leading to a persistently rapid LH pulse frequency, impaired FSH production and inadequate follicular development.[71] Serum free testosterone levels were elevated in all PCOS patients, although the total testosterone levels were normal in 42.8% of obese and 13.3% of nonobese patients. It is suggested that obesity is a factor in causing reduction of Testosterone-Estradiol Binding Globulin (TEBG) levels and it might be a contributory factor in the etiology of PCOS.[72] Women with Cushing's syndrome with higher cortisol secretion may develop hypogonadotrophic hypogonadism. However, even in the latter group, high ovarian volumes were maintained and some had ovarian morphology suggestive of PCOS.[73] Compared with the non-PCOS group, the PCOS subgroup without hirsutism had statistically significantly higher median values of LH, testosterone, androstenedione, and dehydroepiandrosterone sulphate concentrations and free androgen index. Concentrations of androgen, but not LH, were significantly higher still in the PCOS subgroup with hirsutism.[74]

PCOS and Hirsutism

Hirsutism represents a primary clinical indicator of androgen excess. The most common endocrine condition causing hirsutism is PCOS. Obesity associated reproductive and metabolic dysfunctions may aggravate the symptoms of PCOS and it may be underdiagnosed in non obese women because lean PCOS phenotypes might be underestimated for the syndrome. Effective medical treatment of PCOS and associated hirsutism depends on the endocrinological expertise and experience of the therapist in each individual case. An algorithm for the treatment has not been established yet.[75] Cosmetic procedures and pharmacological intervention are commonly used in the treatment of hirsutism and are discussed. Importantly, there are different phenotypes of women with hirsutism and PCOS that may require specific attention in the choice of treatment. In particular, when obesity is present, lifestyle intervention should always be considered, and if necessary combined with pharmacotherapy.[76]

Hirsutism had the strongest impact on the health-related quality of life measures in Iranian women diagnosed with PCOS. Health care officials need to evaluate in depth the effect of each clinical feature of PCOS separately and design management strategies, keeping in mind the psychological and physical manifestations.[77] PCOS is presented by a broad spectrum of menstrual irregularities appearing often at puberty or later on during the reproductive years in women suffering from this multifaceted syndrome. Timing of menstrual irregularities, do not appear to have an impact on hormonal/metabolic profile and ovarian ultrasound morphology in patients diagnosed with PCOS, later in life.[78] After complete clinical, ultrasonographic and biochemical evaluation, it was revealed that PCOS is common in rural young women of low socioeconomic class. Such women presenting with menstrual irregularities need to be investigated particularly with respect to a family history of hypertension, diabetes and menstrual irregularities in their mothers. A state of hyperinsulinaemia indicated by a low FPG to insulin ratio was present, even in non-obese women with PCOS.[79] Women with PCOS and overt oligomenorrhea comprise the vast majority of PCOS subjects seen clinically and have significantly had more IR than controls. About 20% of PCOS women seen reported vaginal bleeding intervals of fewer than 35 days in length and did not generally have overt IR, regardless of whether they were ovulatory or not.

Overall, the presence of clinically evident menstrual dysfunction can be used to predict the presence and possibly the degree of IR in women with PCOS.[80]

PCOS and Menstrual disturbances

Screening for menstrual irregularity, obesity and signs of clinical hyperandrogenism for early diagnosis of PCOS in an effort to improve the reproductive health of adolescent girls.[81] Menstrual irregularity and/or elevated androgen levels are already present in adolescence in women with PCOS and infertility in later life, which strengthens the importance of early identification of menstrual irregularity.[82] Management of clinical manifestations of PCOS includes oral contraceptives for menstrual irregularities and hirsutism and spironolactone and finasteride are used to treat symptoms of androgen excess. Treatment options for infertility include clomiphene, laparoscopic ovarian drilling, gonadotropins, and assisted reproductive technology.[83] Pre-existing menstrual abnormalities predicted higher levels of 17 alpha-OH progesterone, free testosterone and estrone as well as development of new menstrual abnormalities. BMI was significantly positively correlated with free testosterone levels and IR across all subjects, regardless of medication used. Rates of menstrual disturbances are high in women with bipolar disorder and, in many cases, precede the diagnosis and treatment for the disorder. Treatment with valproate additionally contributes significantly to the development of menstrual abnormalities and an increase in testosterone levels over time. A number of bipolar women, regardless of type of medication treatment received, have reproductive and metabolic hormonal abnormalities, yet the etiology of such abnormalities requires further study. Women with pre existing menstrual abnormalities may represent a group at risk for development of reproductive dysfunction while being treated for bipolar disorder.[84]

CONCLUSION

PCOS is an universal health problem occurring in approximately 5 to 20% of females worldwide and among 20% in adolescents Indians of reproductive age. Vitamin D & Calcium deficiencies, IR due to T2DM together with over production of androgens have been cited as principal factors contributing to the development of PCOS. The etiology of the causes are still under extensive investigations. This review article highlights the outcome of research findings in this field during the last two decades, especially from 2000 till date, linking laboratory diagnosis to PCOS, bringing out the usefulness of Vitamin D, Calcium and Magnesium along with the effect of alterations in the levels of Prolactin, LH & FSH. T2DM and the various treatment options especially Metformin along with Vitamin D and Calcium supplements in part or whole have been suggested as remedies for PCOS. Further studies in this filed will certainly help to establish a set of routine clinical laboratory tests to aid obstetricians for the total diagnosis towards solid treatment options.

Conflict of Interest: None.

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