ISSN (Online) 2456 -1304

International Journal of Science, Engineering and Management (IJSEM)
Vol 6, Issue 1, January 2021

SPECTRUM OF CONSEQUENCES OF POLYCYSTIC OVARIAN SYNDROME: A REVIEW

[1] Dr. Soumee Das Samanta, [2] Dr. Dipan Samanta
[1][2] MBBS, Post Graduate Trainee (Dali University, China)

Abstract: **- Polycystic Ovary Syndrome (PCOS) is basically a heterogenous endocrinological disorder occurs in females of reproductive ages. It is mostly associated with metabolic abnormalities. As a hallmark, a combination of anovulation and androgen excess is considered as an important diagnostic criteria for PCOS. Although the etiology of PCOS is need to be further explored, currently we use combination of clinical and biochemical features to come to the conclusion of PCOS. As PCOS is quite prevalent in female of reproductive age, our study explored other more studies to review their findings. There are some evidences of PCOS with other diseases like Type 2 Diabetes Mellitus and Thyroid disorders. This study has reviewed other epidemiological studies to conclude the findings of the associated diseases with PCOS. PCOS and associated problems can exhibit a wide range of manifestations which are found to have positive associations with Hyperandrogenemia, Infertility, Diabetes, Obesity related Cardiovascular problems, Endometrial Cancer and even Breast Cancer. All these possibilities and Etiological aspects have been stated in this study. These manifestations often form a vicious cycle as presented in Fig. 1 and become very challenging job for the Physician to manage it therapeutically. For an effective and successful Management of PCOS, its very important to find out the exact cause which can vary from case to case. We, in our study, have discussed different Etiological factors of PCOS along with their respective complications. Moreover, the scope of further Study and Medical Researches have been highlighted meticulously.**

INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine cum reproductive disorder caused by primary hyperandrogenism and oligoanovulation in the females of reproductive age and is often associated with infertility, clinical and metabolic disorders. Its prevalence is said to be between 5% and 13% in women of reproductive age (1).

Rotterdam criteria are the broadest combinations of unexplained clinical or biochemical evidence of hyperandrogenism, evidence of oligo-anovulation and Polycystic Ovarian Morphology (PCOM). According to Androgen Excess - PCOS Society (AE-PCOS) criteria (2006), PCOS can be presented with anovulatory symptoms (along with hyperandrogenism) which is called as ovulatory PCOS. Therefore, a woman can be diagnosed as PCOS who are with hyperandrogenism and lack anovulatory symptoms. This kind of patients comprises about 10% of cases (2). PCOS is a multifactorial disorder, mostly with a genetic underlying cause. Near about 20% to 40% of first degree female relatives of the patient develop PCOS. As compared to this data, among general population, this percentage varies between 4% to 6%. Other diseases like type 2 diabetes, contribute in the development of PCOS. Some studies involving genome wide association have successfully identified particular genes that are involved in the etiology of PCOS (19).

The studies done on the genome of Chinese population (Genome Wide Association Studies or GWAS) have concluded several loci leading to the mapping of genes like DENND1A, THADA, LHCGR, FSHR, INSR, TOX3, YAP1, RAB5B, c9orf3, HMGA2, and SUMO1P1/ZNF217. These genes are said to have involvement in gonadotropin action and regulation, steroidogenesis, follicular development, calcium signaling and even endocytosis, insulin signaling and type 2 diabetes mellitus (20).

The authors of this study reviewed the diagnostic criteria, other literatures and presented the current epidemiological scenario of the disorder and also stated the need of further research.

Polycystic Ovary Syndrome (PCOS) gained public health importance as it affects one in five females of reproductive age. PCOS has various clinical features which includes infertility, increased androgen, increased androgenic hair growth, insulin resistance, increased cardiovascular risk, anxiety and depression. Hence this syndrome requires multi disciplinary management options including support, education, reducing the body weight, managing the

ISSN (Online) 2456 -1304

International Journal of Science, Engineering and Management (IJSEM)
Vol 6, Issue 1, January 2021

underlying cause like insulin resistance and addressing the psychological factors (21).

DIAGNOSTIC CRITERIA

There are various criteria on which diagnosis is done. During early years of puberty, symptoms of PCOS start. As both the normal female pubertal development and PCOS features are characterized by irregular menstrual cycles, anovulation, and acne, it is quite difficult to identify the onset of PCOS among young pre-pubertal girls, at early stage. The data that is available are linked to the findings among adult women of reproductive age. As of now, the "Rotterdam criteria" is accepted for adult women as for standard diagnostic procedure. The most common features of PCOS for adolescent girls are menstrual irregularity, clinical hyperandrogenism, and/or hyperandrogenemia. Pelvic ultrasound findings are not essential for the diagnosis of PCOS in adolescent girls. Before definitive diagnosis, adolescent girls with clinical signs of androgen excess and oligomenorrhea or amenorrhea can be considered as population at risk of PCOS (18).

As mentioned earlier, there are many criteria for diagnosing PCOS (Refer to Table 1). One of the most acceptable is Rotterdam European Society of Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM) - Sponsored PCOS Consensus Workshop Group (8), which have put forward a broader definition of PCOS and diagnostic criteria as two out of three of the following criteria should be present to make a diagnosis:

1. polycystic ovaries (either 12 or more follicles or increased ovarian volume [> 10 cm3])
2. oligo - ovulation or anovulation
3. clinical and/or biochemical signs of hyperandrogenism.

They have also said that diagnosis should be made when some of the other etiologies of disturbed menstrual cycle are excluded, like thyroid dysfunction, acromegaly or hyperprolactinemia. Hyperandrogenism can include hirsutism (excess facial and body hair along with midline hair growth). Free androgen index (Total testosterone/SHGB X 100) is treated as the standard biochemical test for determining hyperandrogenism along with free and total testosterone. Exclusion of other conditions like androgen secreting tumors and Congenital Adrenal Hyperplasia (CAH) should be excluded if signs of virilisation, rapid hirsutism or high level of testosterone (like more than 5 nmol/l or more than twice the upper limit of normal reference range). Also, high level of 17-hydroxyprogesterone is attributed to CAH. Signs of Cushing's syndrome or acromegaly should be investigated as per national/local practice guidelines. Measurement of androgen should be done preferably by Tandem Mass Spectrometry (TMS) (3).

Prevalence:

Being hetergeneous disorder, PCOS affects at least 7% of adult women. According to the data of National Institutes of Health Office of Disease Prevention, USA, approximately 5 million women of reproductive age in the USA are being affected by PCOS. Near about 4 billion USD per year is spent in USA for identification and management of PCOS. The study suggests that 5% to 10% of females between 18 to 44 years of age are affected by PCOS and can be consider as the most common endocrinological abnormality among females of reproductive age in the USA. The authors also stated that female patients of reproductive age who come in the clinic with obesity, acne, amenorrhea, excessive hair growth, and infertility often receive a diagnosis of PCOS (17).

In a "cross - sectional community - based study" was done in India in order to understand the prevalence of PCOS in urban setting. The study was carried out on 778 adolescents girls between the age of 15 - 24 years old. The researchers used clinical investigations, ultrasonography and biochemical tests and subsequently found the results 22.5% and 10.7% of the total participants have PCOS, according to Rotterdam criteria and Androgen Excess Society criteria, respectively. The researchers found the most common phenotype (52.6%) was Mild PCOS (oligomenorrhea and polycystic ovaries as found in Ultrasonography). It had reported that the history of oligomenorrhea had Positive Predictive Value (PPV) of 93.3% and Negative Predictive Value (NPV) of 86.7%, in detection of possible case of PCOS. In addition, 19.2% of diagnosed PCOS cases have hyperinsulinemia whose serum insulin > 15 µlU/mL. (4).

CLINICAL FEATURES AND COMPLICATIONS

Some of the clinical features that are found promptly in this syndrome are hirsutism, acne and seborrhea, androgenic alopecia, Onycholysis and Onychorrhexis, hyperinsulinemia, insulin resistance and hyperandrogenemia. Hirsutism is characterized by excessive terminal hair in the androgen dependent areas and those areas where usually limited hair growth occurs as in face, chest, areolas, abdomen and upper thighs. Although hyperandrogenemia is present, the rate of the hair growth is not proportional to the degree of hyperandrogenism. This shows that the hyperandrogenemia has parallel role in PCOS. This hyperandrogenemia also affects androgen dependent streuctures like sebaceous glands with sebocytes. These cells are highly sensitive to androgen signaling that exacerbate in PCOS resulting in the development of acne and seborrhea. Sebocytes proliferation takes place (especially in midline of back, forehead and chin)

and there is also sebum secretion. This is complicated further by the action of the local bacteria by secreting lypolytic enzymes that break down triglycerides produced in the sebocytes. On the another side, androgen dependent alopecia occurs due to increased telogen:anagen ratio. Increased androgen leads to increased local conversion of testosterone into DHT which is more potent androgen. Nails are also affected in form of onycholysis. Although the consequence of nails cannot be well understood in association of excessive androgen presence in PCOS. The association of Insulin Resistance, Hyperinsulinemia and Hyperandrogenemia is thoroughly studied. All these pathological conditions have been proved by the fact that insulin sensitizing pharmacotherapy that lowers androgenemia, improves the ovarian function in a patient of PCOS. The authors also mentioned important roles of insulin in order to explain the development of the increased amplitude and frequency of the hormones GNRH and LH pulse secretion, as found in PCOS. Insulin may stimulate GnRH gene transcription through MAPK pathway leading to increased secretion of GnRH from hypothalamus. Subsequently there is secretion of LH which later translated into ovarian steroid hormones, especially androgens. Menstrual irregularities and anovulation become quite prevalent in PCOS patients who are specially obese as compared to the nonobese PCOS patients. Infact, it has been seen that loss of atleast 5% improves the condition of PCOS.

A study done by Fite, L.P. and Cohen, P.R. (2017), seldom reported that the dermatologic manifestations among young patients are confluent and reticulated papillomatosis characterized by hyperkeratotic and verrucous papules that coalesce into plaques centrally and form a reticular pattern at the periphery. It is a rare dermatosis of unknown etiology. For an instance, the authors of this study presented a case of young age with obesity, confluent and reticulated papillomatosis and concurrent acanthosis nigricans. Perivascular lymphocytic inflammation is found in small amount and dilation of superficial vessels were found in the dermis layer of the skin (5).

Leptin, known as the prototypical adipokine, is a 167 amino acid peptide secreted primarily from white adipose tissue, although it is present at several other sites, including the ovary Leptin stimulates the secretion of LH, as can be said by improvement of LH pulses following leptin administration in women with fasting-induced HHOA dysfunction. Leptin also has direct effects in all ovarian cells and said to have a physiologic regulatory effect in the process of folliculogenesis. Some of the recent findings say that proinflammatory mediators have role in the pathophysiology of PCOS. Hence PCOS is now considered as a chronic, low grade inflammatory disorder which can aggrevate in obesity and is not directly related to obesity. PCOS patients, whether obese or non-obese, have shown to have elevated serum TNF, CRP, monocytes and lymphocytes and ovarian tissue are invaded by inflammatory cells. There are many suggestion passed in this regard. One of them is the existence of proinflammatory genotypes including polymorphisms of sequences that are coding TNF, TNF receptor, IL-6, and IL-10. Again, greater expression of the CD11c gene is associated with greater proinflammatory macrophage infiltration. This study also mentions that the cytokine's role in stimulation of steroidogenesis as well as follicular atresia and its contribution to hyperandrogenemia, again, leading to self-perpetuation for PCOS (6).

In another study, the authors marked PCOS as a risk factor for type 2 diabetes mellitus and also gestation diabetes. They mentioned 1 in 5 PCOS patients may develop Type 2 diabetes and it implies that glucose tolerance impairment is a common abnormality in this disease. In fact, both cross-sectional and prospective longitudinal studies have shown PCOS patients to have higher risk of developing type 2 diabetes mellitus or atleast impaired glucose tolerance compared to the control, in the same ethnicity and age group. Needless to say, positive family history of diabetes also contributes in resulting diabetes mellitus type 2 among PCOS patients. Recent data have shown significant elevated levels of circulating biomarkers of Cardiovascular disease including C-reactive protein and lipoprotein A, compared to matched controls. In the year 2010, Androgen Excess - PCOS society had provided a consensus statement regarding the increased risk of Cardiovascular disease among PCOS patients and developed a guidelines in order to prevent such complications. It has been seen that PCOS patients have reduced fertility due to associated endocrine and gynaecologic abnormalities leading to poor ovarian quality and function. In 90% of ovulatory disorders, PCOS associated persistent periods of anovulation are correlated positively with infertility. This study also mentions another study that concluded 50% of PCOS patients and 25% of PCOS patients are suffering from primary and secondary infertility respectively. There is a need of further study to determine the degree of infertility among PCOS patients and conclude the reasons for increased pregnancy outcomes in this group of women. Regarding cancer, PCOS patients are found to be more risky in developing endometrial cancer like obesity, insulin resistance, type 2 diabetes mellitus and anovulation. Due to anovulation, unopposed uterine estrogen exposure is presented and can lead to the development of endometrial hyperplasia and endometrial cancer. There is limited data and facts available to support any kind of association with breast and ovarian cancer among PCOS patients. The authors of this study suggests further research

in this regard (7).

In another study, polycystic ovarian syndrome (PCOS) is one of the most common endocrinopathy among females of reproductive age. It is estimated to have prevalence almost about 10%. There are various symptoms that can be found in this syndrome and it varies from patient to patient. It is quite obvious that due to the complexity of the syndrome, a number of metabolic and other abnormalities may arise in the near future. PCOS also found to have a long prodrome phase with the detectable abnormalities. Almost 25% to 30% of women having PCOS also found to have glucose intolerance by the age of 30 and 8% of women with PCOS will later develop Type 2 diabetes mellitus annually. The authors of this study also inferred that the patients of PCOS experience more extensive coronary artery disease which is evidenced by angiography and also hypertension. Long term anovulation leads to increased risk of endometrial cancer, ovarian cancer and even breast cancer (9).

In a study Brigham and Women's Hospital and Harvard Medical School, Boston, MA USA, the authors of the said study showed the association between PCOS and endometrial cancer from 11 individual studies and 3 meta analyses. The authors also reviewed 8 individual studies and 1 meta analysis for showing association between PCOS and ovarian cancer and 10 studies and 1 meta-analysis for breast cancer. Although, the association with ovarian cancer was less clear, there is increased risk of ovarian cancer (borderline serous subtype), as reported by two studies (10). In another study conducted in University of New South Wales, Sydney, Australia, the authors reviewed the current evidence on managing PCOS patients, specially in adolescent groups. More over, this study summarised the pathophysiology, risk factors, clinical presentations and existing diagnostic criteria of PCOS. According to them, clinicians have less risk factors to identify the adolescents who are at risk of PCOS and so the diagnosis cannot be done at early stage. The authors stated that PCOS can lead to infertility, type 2 diabetes mellitus, cardiovascular disease and even endometrial cancer. The authors also emphasised that the lifestyle modification is of the greatest beneficial factor for adolescents in terms of management of PCOS. The authors also mentioned the psychological impact of PCOS is one of the major concern in adolescent PCOS, in this generation (11). In one study done by group of scientists, stated that analysis of predisposing conditions of PCOS including genetic cause and environmental factors, like endocrinological abnormalities and lifestyle, all should be analysed further to make association with PCOS. Animal studies have supported and concluded that early exposure to sufficient androgen excess, can be associated with Insulin resistance. The authors also said that PCOS have long term consequences in development of type 2 diabetes, cardiovascular diseases and hormone dependent cancers (12). The pathophysiology of PCOS includesuncontrolled ovarian steroidogenesis, aberrant insulin signaling, excessive oxidative stress, and genetic/environmental factors. In PCOS, hyperandrogenemia is caused by an intrinsic defect in theca cells. PCOS patients have theca cells which secrete androgens in large amount due to an intrinsic activation of the process of steroidogenesis, even in the absence of trophic factors. In PCOS, affected granulosa cells produce anti-mullerian hormone (AMH) 4 times higher than normal as compared to healthy controls. More over, decreased insulin sensitivity attributable to a post - receptor binding defect in the insulin signaling pathways is one of the intrinsic component of PCOS. PCOS patients with a susceptible genetic component, can lead to signs of premature pubarche, premature adrenarche (elevated DHEAS), and metabolic syndrome (insulin resistance and visceral adiposity). The authors suggested supplementary studies are definitely required to shed light over the missing links between the ovarian dysregulation, androgen excess, genetics, and various susceptibility factors that might contribute to PCOS (13).Basically, PCOS can be considered as hormonal disorder which has potential to lead to various abnormalities including some diseases. PCOS is one of the most common cause of infertility in female population. The three most common features associated with PCOS are irregular ovulation, increased levels of androgen and cystic ovaries. Apart from these features, hirsutism, acne and alopecia are directly associated with increased levels of androgen and the prevalence of polycystic ovaries observed when pelvic ultrasound is done, found in more than 70% of PCOS (14). In another study, it is stated that PCOS affects 5% to 10% of females of reproductive age. Also, the authors consider PCOS as the most common cause of anovulation in infertile females. PCOS is accompanied by absence of ovulation, hyperandrogenism, decreased cell sensitivity to insulin. hyperlipidaemia, even obesity. Each of these factors are also approved risk factors predisposing to cancer. The authors of this study also made an important statement that all the features are not shown by a particular patient of PCOS, rather features vary from patient to patient. The authors also concluded that there is possible correlation between PCOS and endometrial cancer, which emerges from clinical trials or research focused on molecular changes in endometrium patients with PCOS. Although, the authors could not present a good correlation between PCOS and breast or ovary cancer. The biggest difficulty in studying the correlation between PCOS and risk of any cancer, is the only presence of very small group of females or the trial is imperfect, like lack of control group. There is no meta-

analysis focused on this correlation in literature (15).

DISCUSSION

PCOS is a complex disease featuring groups of symptoms in females of reproductive age. It ranges from ovulation disorders, elevated level of androgen to other endocrinological abnormalities and metabolic disturbances (Refer to Figure 1). PCOS may induce several other abnormalities including infertility, insulin resistance, alopecia, increased bleeding, irregular menstruation, endometrial cancer. Although the treatment is quite largely symptomatic. The exact etiology of PCOS remains unsolved and it is known to consists of several hormonal disturbances, including hyperandrogenemia, hyperinsulinemia and insulin resistance (IR). Insulin appears to disrupt all components of the hypothalamus-pituitary-ovary (HPO) axis and ovarian tissue insulin resistance leading to defective metabolic signaling but mitogenic and steroidogenic activity remain intact. This favors increased level of androgen, which appears to be the main clinical presentation of PCOS (16). Research should be conducted more in hormonal management and there is a need of formulation of management strategies of combined features of PCOS as this disorder is mostly presented as combination of features like hirsutism and obesity, obesity and insulin resistance, etc. Medical managements should be formulated such as to minimize the drugs' interaction, as well. There is also need of formulating preventive strategies for the girls of pre - reproductive ages.

The authors of this study also recommend that there is a need of further studies regarding PCOS with infertility and insulin resistance, in the future. The associations between PCOS and endometrial, ovarian and breast cancer separately, are not clearly explained and so, there is a need of methodological studies in future. Especially the larger well-designed studies or pooled analyses, are essential to clarify these complex associations.

CONCLUSION

The scope of this study ranges from diagnostic criteria of PCOS to the possible various consequences of a PCOS patient. The diagnostic criteria are laid down in this study from Rotterdam European Society of Human Reproduction and Embryology (ESHRE). The study also put forward the present scenario of prevalence of this disorder. This study also summarised several factors of epidemiology related to PCOS. The author of this study noted several studies revealing various manifestations and consequences of PCOS. There are mentions about papillomatosis and concurrent acanthosis nigricans as dermatologic manifestation. Hyperkeratotic and verrucous papules are also mentioned among several other dermatologic manifestations. The study also mentions hirsutism, androgenic alopecia, hyperinsulinemia, insulin resistance and hyperandrogenemia. This study thoroughly reviews the mechanism of insulin resistance and hyperinsulinemia in PCOS. The study also reviews the role of leptin in this disorder and provides justification of tagging PCOS as inflammatory reaction as well. The study also reviewed PCOS as a risk factor for Type 2 diabetes mellitus along with gestational diabetes. Infertility as a consequence has been widely discussed in this study. Overall, important diagnostic features, detailed epidemiological scenario and various consequences are discussed with a special emphasis on insulin resistance and infertility. This review reveals the various and interlinked features of PCOS.

TABLES AND FIGURES

ISSN (Online) 2456 -1304

International Journal of Science, Engineering and Management (IJSEM)
Vol 6, Issue 1, January 2021

Diagnostic criteria for PCOS (summary)

Year	Diagnostic criteria proposed by	Criteria	Number of criteria required for diagnosis	Phenotype
1990	National Institutes of Health[1]	1.Hyperandrogenism 2.Oligo-anovulation	Two out of two	
2003	Rotterdam's criteria[2,3]	1.Hyperandrogenism 2.Ovulatory dysfunction 3.Polycystic ovarian morphology (12 follicles 2-9 mm in each ovary with volume of 10 ml)	Two out of three	
2006	AE-PCOS[4,5]	1.Hyperandrogenism 2.Ovulatory dysfunction	Two of two	
2012	NIH 2012 extension ofESHRE/ASRM 2003[6]	1.HA 2.OD 3. PCOM	1. Two of three 2. Identification of specific phenotype	A.HA + OD + PCOM B. HA + OD C.HA + PCOM D.OD + PCOM

HA = Hyperandrogenism; OD = Ovulatory dysfunction; PCOM = Polycystic ovarian morphology

Table 1Diagnostic criteria for PCOS put forwarded by several institutes/organization in different times

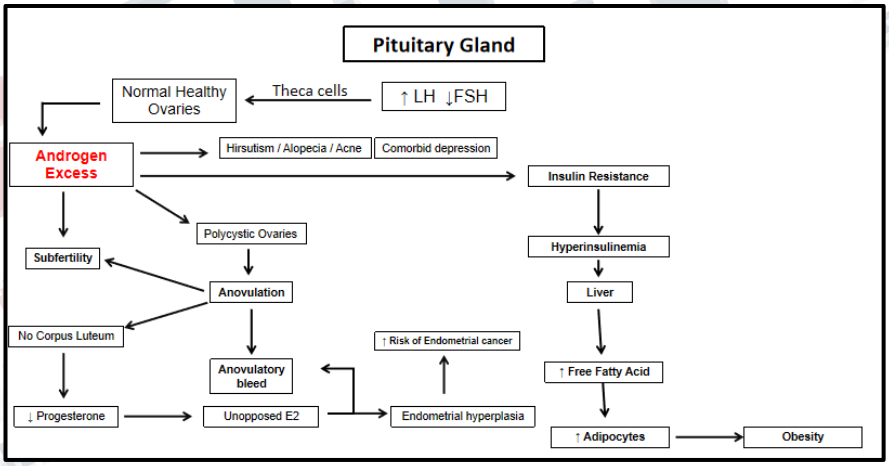

Figure 1Map of endocrinological abnormalities and metabolic disturbances that sequentially occur in PCOS https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5045492/table/T1/?report=objectonly.

References

1. Melo, A., Ferriani, R. and Navarro, P. (2015). Treatment of infertility in women with polycystic ovary syndrome: approach to clinical practice. Clinics, 70(11), pp.765–769.

2. Rosenfield, R.L. and Ehrmann, D.A. (2016). The Pathogenesis of Polycystic Ovary Syndrome (PCOS): The Hypothesis of PCOS as Functional Ovarian Hyperandrogenism Revisited. Endocrine Reviews, [online] 37(5), pp.467–520. Available at:

3. WL Ledger, SL Atkin, The Michael White Diabetes Centre, Dr T Sathyapalan (2014).Long-term Consequences of Polycystic Ovary Syndrome

4. Joshi, B., Mukherjee, S., Patil, A., Purandare, A., Chauhan, S. and Vaidya, R. (2014). A cross-sectional study of polycystic ovarian syndrome among adolescent and young girls in Mumbai, India. Indian Journal of Endocrinology and Metabolism, [online] 18(3), p.317. Available at: http://www.ijem.in/article.asp?issn=2230-

8210;year=2014;volume=18;issue=3;spage=317;epage=324;aulast=Joshi;type=3 [Accessed 18 Aug. 2019].

5. Fite, L.P. and Cohen, P.R. (2017). Polycystic Ovarian Syndrome-associated Confluent and Reticulated Papillomatosis: Report of a Patient Successfully Treated with Azithromycin. The Journal of Clinical and Aesthetic Dermatology, [online] 10(9), pp.30–35. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29344325 [Accessed 10 May 2020].

6. Rojas, J., Chávez, M., Olivar, L., Rojas, M., Morillo, J., Mejías, J., Calvo, M. and Bermúdez, V. (2014). Polycystic Ovary Syndrome, Insulin Resistance, and Obesity: Navigating the Pathophysiologic Labyrinth. International Journal of Reproductive Medicine, [online] 2014, pp.1–17. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4334071/.

7. El Hayek, S., Bitar, L., Hamdar, L.H., Mirza, F.G. and Daoud, G. (2016). Poly Cystic Ovarian Syndrome: An Updated Overview. Frontiers in Physiology, [online] 7. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4820451/.

8. Shalini Gainder and Sharma, B. (2019). Update on management of polycystic ovarian syndrome for dermatologists. Indian Dermatology Online Journal, [online] 10(2), p.97. Available at: http://www.idoj.in/article.asp?issn=2229-5178;year=2019;volume=10;issue=2;spage=97;epage=105;aulast=Gainder [Accessed 9 Jul. 2019].

9. Daniilidis, A. and Dinas, K. (2009). Long term health consequences of polycystic ovarian syndrome: a review analysis. Hippokratia, [online] 13(2), pp.90–2. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2683463/.

10. Harris, H.R. and Terry, K.L. (2016). Polycystic ovary syndrome and risk of endometrial, ovarian, and breast cancer: a systematic review. Fertility Research and Practice, [online] 2(1). Available at: https://fertilityresearchandpractice.biomedcentral.com/articles/10.1186/s40738-016-0029-2 [Accessed 23 Mar. 2019].

11. Yii, M.F., Lim, C.E.D., Luo, X., Wong, W.S.F., Cheng, N.C.L. and Zhan, X. (2009). Polycystic ovarian syndrome in adolescence. Gynecological Endocrinology: The Official Journal of the International Society of Gynecological Endocrinology, [online] 25(10), pp.634–639. Available at: https://pubmed.ncbi.nlm.nih.gov/19533479/ [Accessed 30 Jul. 2020].

12. Pasquali, R., Stener-Victorin, E., Yildiz, B.O., Duleba, A.J., Hoeger, K., Mason, H., Homburg, R., Hickey, T., Franks, S., Tapanainen, J.S., Balen, A., Abbott, D.H., Diamanti-Kandarakis, E. and Legro, R.S. (2011). PCOS Forum: research in polycystic ovary syndrome today and tomorrow. Clinical Endocrinology, 74(4), pp.424–433.

13. El Hayek, S., Bitar, L., Hamdar, L.H., Mirza, F.G. and Daoud, G. (2016). Poly Cystic Ovarian Syndrome: An Updated Overview. Frontiers in Physiology, [online] 7. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4820451/.

14. Ndefo, U.A., Eaton, A. and Green, M.R. (2013). Polycystic ovary syndrome: a review of treatment options with a focus on pharmacological approaches. P & T : a peer-reviewed journal for formulary management, [online] 38(6), pp.336–55. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3737989/.

15. Jakimiuk, A.J. and Issat, T. (2009). PCOS and cancer risk. Folia Histochemica et Cytobiologica, [online] 47(5), pp.101–105. Available at: https://journals.viamedica.pl/folia_histochemica_cytobiologica/article/view/4280 [Accessed 31 Jul. 2020].

16. Rojas, J., Chávez, M., Olivar, L., Rojas, M., Morillo, J., Mejías, J., Calvo, M. and Bermúdez, V. (2014). Polycystic Ovary Syndrome, Insulin Resistance, and Obesity: Navigating the Pathophysiologic Labyrinth. [online] International Journal of Reproductive Medicine. Available at: https://www.hindawi.com/journals/ijrmed/2014/719050/.

17. Ndefo, U.A., Eaton, A. and Green, M.R. (2013). Polycystic ovary syndrome: a review of treatment options with a focus on pharmacological approaches. P

& T : a peer-reviewed journal for formulary management, [online] 38(6), pp.336–55. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3737989/.

18. Witchel, S.F., Oberfield, S.E. and Peña, A.S. (2019). Polycystic Ovary Syndrome: Pathophysiology, Presentation, and Treatment With Emphasis on Adolescent Girls. Journal of the Endocrine Society, [online] 3(8), pp.1545–1573. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6676075/.

19. Dennett, C.C. and Simon, J. (2015). The Role of Polycystic Ovary Syndrome in Reproductive and Metabolic Health: Overview and Approaches for Treatment: TABLE 1. Diabetes Spectrum, [online] 28(2), pp.116–120. Available at: https://spectrum.diabetesjournals.org/content/28/2/116.

20. Dadachanji, R., Shaikh, N. and Mukherjee, S. (2018). Genetic Variants Associated with Hyperandrogenemia in PCOS Pathophysiology. [online] Genetics Research International. Available at: https://www.hindawi.com/journals/gri/2018/7624932/ [Accessed 2 Aug. 2020].

21. H, T., A, D. and L, M. (2010). Polycystic Ovary Syndrome: A Complex Condition With Psychological, Reproductive and Metabolic Manifestations That Impacts on Health Across the Lifespan. [online] BMC medicine. Available at: https://pubmed.ncbi.nlm.nih.gov/20591140/.