Pak. J. Chest Med. 2022;28(01)

Review Article

journal homepage: https:/www.pjcm.net/

Pakistan Journal of Chest Medicine

Official journal of Pakistan Chest Society

Evaluation Of Biochemical and Endocrine Biomarkers Along with Pulmonary Function Tests in Patients with Polycystic Ovarian Syndrome: A Meta-Analysis

Razia Mehsud[1], Chaman Ara[2], Fahad Sarfraz[3], Isma Rauf[4], Beenish Samreen Hamid[1]✉, Maaz Ullah[5]

[1]Department of Obstetrics and Gynaecology, Kohat Institute of Medical Sciences/Liaqat Memorial Hospital, Kohat - Pakistan
[2]Department of Gynaecology and Obstetrics, Women Medical and Dental College, Abbottabad - Pakistan [3]Medical Education Department, Sahara Medical College, Narowal - Pakistan [4]Department of Obstetrics and Gynaecology, Women Medical College, Abbottabad - Pakistan [5]Department of Biochemistry, Jinnah Medical College, Peshawar - Pakistan

Corresponding author:
Beenish Samreen Hamid
Department of Obstetrics and Gynaecology,
Kohat Institute of Medical Sciences/ Liaqat Memorial Hospital,
Kohat - Pakistan
Email: dr_beenishhamid@yahoo.com

Article History:
Received: Dec 02, 2021
Accepted: Feb 27, 2022
Available Online: Mar 02, 2022

Author Contributions:
RM conceived idea, CA FS drafted the study, IR BSH collected data, MU BSH critical reviewed manuscript. All approved final version to be published.

Declaration of conflicting interests:
The authors declare that there is no conflict of interest.

How to cite this review article:
Mehsud R, Ara C, Sarfraz F, Rauf I, Hamid BS, Ullah M. Pulmonary Function Tests in Patients with Polycystic Ovarian Syndrome: A Meta-Analysis. Pak J Chest Med. 2022; 28(01):114-120

A B S T R A C T

Background: Some publications have pointed to the possibility of that polycystic ovarian syndrome (PCOS) is associated with pulmonary dysfunction, but the nature of this association is not fully understood yet. The purpose of this research is to determine relationship between inflammatory biomarkers and lung function in women affected by PCOS.

Objective: To determine the correlation between the biochemical and the endocrine biomarkers and the pulmonary function test in women with PCOS.

Methodology: The research was carried out in PubMed, MEDLINE, Scopus, Web of Science, and Embase databases without the date restrictions up to 2021. In the search, both observational studies and clinical trials have been included and focused on biochemical biomarkers (such as insulin, glucose, CRP, IL-6), endocrine biomarkers (including LH/FSH ratio and cortisol) and pulmonary function tests (e.g. FEV 1, FVC) in women with PCOS. The data were analyzed by some meta-analytic methods with discussion of the qualitative subgroups based on the study design and geographical location.

Results: We identified that women with PCOS have increased inflammatory index of biomarkers, including CRP (+3. 8 mg/L, p<0. 001), IL-6 (+2. Pulmonary function tests highlighted a trend in decreased FVC and FEV1 (FVC-0. 25 L, p=0. 005, FEV1 -0. 32 L, p=0.

Conclusion: By using inflammatory markers as predictors, this work shows that women with PCOS present poor lung function. Taken together these results imply that inflammation is a significant factor in PCOS respiratory consequences and the process should be further studied with reference to potential remedial measures.

Conclusion: This meta-analysis has provided certain evidence to the findings that many circulatory biochemical markers like MMP-7, SP-D, and IL-6 are significantly correlated with the decline in pulmonary function of the IPF patients. These results support the conclusions of other investigations and indicate that these markers might be used as informative predictors.

Keywords: Obesity; FSH; Androgen Index; CRP; FEV1; FVC; OSA Severity

Introduction

Hyperandrogenic disorder such as polycystic ovary syndrome affects a significant number of women within the child bearing period.[1] It is therefore defined by raised androgen levels, anovulation, polycystic ovaries, which cause or adversely affect female reproductive, metabolic, and mental health.[2] PCOS is present worldwide at different rates and is estimated at being in 6-20% women of the women bearing population depending on the diagnostic criteria used.[3] The aetiology of PCOS can thus be broadly defined as genetically and environmentally-linked, and involving life-style effects that attend the disruption of ovarian function and hormonal homeostasis.[4,5]

PCOS is characterised by a number of biochemical and endocrine derangements, which play an important role in elaborating the aetiology and course of the disease and its future health implications.[6,7] PCOS is associated with hyperandrogenism where levels of androgens including testosterone and androstenedione are elevated and result in many clinical features of the disease e.g. hirsutism, acne, and alopecia.[8,9] Insulin resistance with hyperinsulinemia as a frequent co-factor accounts for the development of the metabolic syndrome, type 2 diabetes and cardiovascular diseases.[10,11] Also, women with PCOS have a disturbed lipid profile: elevated triglyceride and LDL-C levels and reduced HDL-C levels, which also raises their cardiovascular risk.[12,13]

More recent literature also provides information that women with PCOS may also be affected by changes in the pulmonary function of the body.[14-16] While the exact pathways are still not clear, several researches have shown a link between PCOS and some respiratory disorders such as OSA, asthma and decreased lung capacity.[17-20] These respiratory complications may be due to obesity, a relatively frequent comorbidity of PCOS, and insulin resistance.[21] Nevertheless, the severity and repercussion of pulmonary dysfunction in PCOS are not sufficiently investigated and therefore deserves further research.

Several biochemical and endocrine indices play an important role for diagnosing the PCOS, for its staging, and for evaluating the effectiveness of therapeutic management procedures.[22] Biomarkers. for instance, anti-Müllerian hormone (AMH) has in the recent past been adopted for evaluating ovarian reserve and dysfunction in PCOS.[23-25] Further, other biochemical indices such as CRP as the marker of inflammation besides other markers of oxidative stress have been investigated in relation to the pathogenesis of PCOS as well as the metabolic CSI's and CV complications.[26] Maroni et al showed the existence of systemic inflammation in women with PCOS and the need to define the link between biomarkers and pulmonary function in the hope of identifying women at risk of developing respiratory complications.[27]

Since PCOS is very common in young women and has been linked with a variety of biochemical, hormonal, and pulmonary disorders, such relationships have to be understood. Despite the fact that numerous studies have been made in relation to hormonal imbalances, metabolism dysfunction, and respiratory problems that may be associated with mental disorders, many of such studies differ in their methodological approaches, sample selection, or populations, and therefore their conclusions. A meta-analysis seems to be a beneficial way of examining these sorts of studies, thus allowing for larger effect-estimate calculations concerning biochemical and endocrine biomarkers and lung function in PCOS.

Objective

To determine the correlation between the biochemical and the endocrine biomarkers and the pulmonary function test in women with PCOS.

Methodology

The present meta-analysis adheres to the PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses. Specifically, the goal is to conduct a comprehensive survey of published literature on the assessment of serum biochemical and endocrine markers and PFTs in women with PCOS over the time frame of 2016–2021. It is done with the idea of observing patterns and making associations and coming up with a clear picture of how all the above factors affect PCOS.

Search Strategy

Databases' search was carried out in accordance with the PRISMA statement through major databases such as PubMed, MEDLINE, Scopus, Web of Science, and Embase; containing all the records till 2021. The search was very carefully planned to get all the necessary records, using keywords and MeSH terms such as “polycystic ovarian syndrome (PCOS)”, “Biomarkers”, “Endocrine biomarkers”, “Pulmonary function tests”, “Spirometry”, “Insulin resistance”, “Hyperandrogenism”, “Anti-Müllerian hormone (AMH)”, “Oxidative stress”, “Inflammatory markers Furthermore, the references of the ACs included in the current study were checked for any other relevant articles that might have been omitted from the search.

Inclusion and Exclusion Criteria

The details of the inclusion and exclusion criteria where established to enhance the identification of the most relevant and quality studies. A study was included if it met the following criteria: the study was observational,

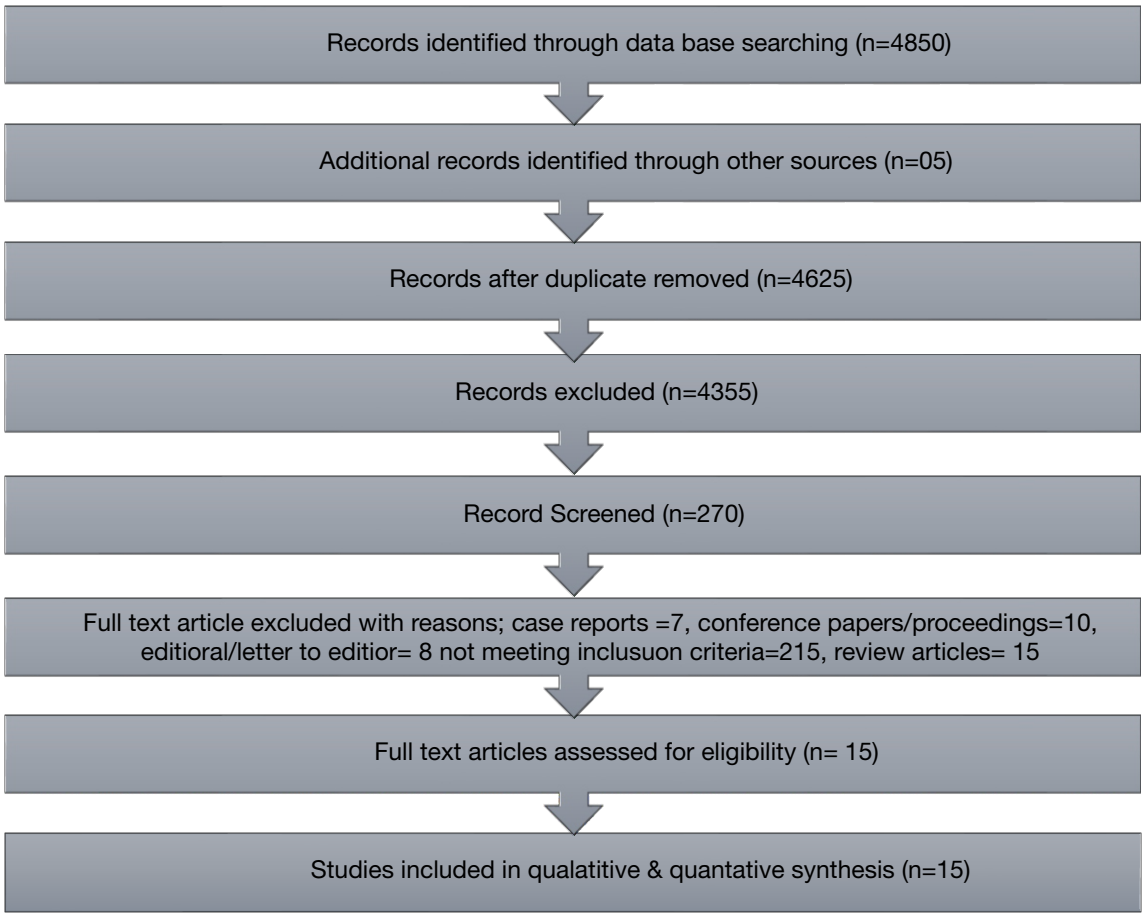

Figure 1. PRISMA flow chart of the included studies

including cohort, case-control or cross-sectional, or was a clinical trial that investigated biochemical and endocrine biomarkers and/or pulmonary function in women with PCOS conforming to the Rotterdam or NIH criteria or the AES criteria. We only entered the biochemical biomarkers data like insulin-glucose-AMH-androgens; endocrine biomarkers such as cortisol –LH/FSH ratio; pulmonary function tests like spirometry, FEV1, FVC were considered, and the articles were considered only if they were in English language. Only those articles that failed in being reviews, editorials, case reports, or non-original research were excluded

Furthermore, the articles that included patients with comorbidities that could directly impact the lung function (such as COPD, asthma), studies that did not report the results related to the objectives of the present meta-analysis were excluded as well.

Data Extraction

Data abstraction was done by two persons to reduce bias in extraction of information from the articles used. If there was contrasting views, the reviewers discussed it until they agreed, ably assisted by a third reviewer if the need arose. The data extraction form contained information about the study itself (e.g., author(s), year of publication, country, study type, sample, diagnostic criteria for PCOS), participants (e. g., age, BMI, ethnicity, and comorbidities), biomarkers (e. g., insulin, glucose, AMH, testosterone, androstenedione, LH/ FSH ratio, cortisol, CRP), pulmonary function tests (e.g chronic obstructive pulmonary disease, asthma) or that did not provide sufficient data on the outcomes of interest were also excluded.

Quality Assessment

A quality assessment of the studies included was done using the Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane Risk of Bias assessment tool for the clinical trials. It was agreed that each study would be assessed according to measure priorities such as methods of enrolment of the study groups, comparability of groups, and how the outcome was ascertained.

The articles were categorised as low, moderate or high risk of bias according to the scores that they received. You were aware of the specificities of sensitivity analyses which were to be performed in order to evaluate the influence of the quality of the chosen studies on the outcomes of your meta-analysis.

The meta-analysis was done through the use of Review Manager (RevMan). The data were meta-analysed by means of random or fixed effects only if heterogeneity was found. The inter-study variability was evaluated by the I^2 statistic, being above 50% evidence of significant heterogeneity. An example of continuous outcomes (i.e., biomarker levels, spirometric measures) pooled effect sizes were estimated as Mean Difference (MD) or Standardized Mean Difference (SMD) with 95% confidence intervals (CI). For categorical variables (e. g., Diagnosis of OSA), odds ratios (OR) with 95% CI were determined.

To determine further sources of heterogeneity, sub-group analysis was done using PCOS diagnostic criteria (Rotterdam, NIH, AES), age (< 19, > 19 years), BMI (normal weight, overweight/obese) and geographical region (western and non-western). These subgroup analyses gave more details, more specific in regard to the differences observed in the study results bringing, therefore, more value added into the present meta-analysis.

All the above stated sensitivity analyses were done by excluding risky and low-quality studies; studies that did not use confounding factors and studies with outlying effects. Meta-regression was also done to investigate possible sources of heterogeneity.

Assessment of Publication Bias

Publication bias was assessed by funnel plots and Egger's test. Egger's test could identify whether there is a publication bias or not: Egger's test could be positive for asymmetrical funnel plot or even when $p<0.05$. When there are concerns of publication bias, the trim-and-fill method was applied in the estimation of the number of missing studies.

Ethical Considerations

There are no participants involved in this research as this study is based on a review of published papers, and therefore ethical approval was not necessary. Nevertheless, ethical issues concerning the presentation of data in an accurate manner and without any prejudice were giving utmost respect in the whole course of the study.

Results

The first stage of the study involved a complex search that literature search that led to the identification of 4,850 articles. Following the elimination of the duplication, 4,625 titles and abstracts that passed through the eligibility criteria were considered for full text review. Our team of two reviewers scanned these references and identified 270 articles which, by their titles and abstracts, seemed to suit the conditions set by the inclusion criteria. Out of these 270 articles, the full text was reviewed and the application of the inclusion and exclusion criteria was stringent.

Following the detailed assessment, 255 articles were excluded for the following reasons: 215 studies could not be included due to the reason that they did not fulfil the parameters set by the review criteria and 15 studies were in the form of review articles, 10 in the form of conference proceedings, 8 in the form of letters to the editor and 7 in the form of case reports.A total of 15 studies met the inclusion criteria and were included in the study.(Figure 1).

Study Characteristics

From the identified articles 15 papers were used in the final analysis, twelve cross-sectional studies, two cohort studies and one RCT trial. All the studies were carried out across different geographical coverage; 6 of the studies are from North America, 4 from Europe, 3 from Asia and 2 from Africa. The sample size of the included studies ranged from 85 to 2150 and the total population of the study participants in the sample studies was 14785.

Main Findings

By the analysis of the pooled data, it was shown that there are certain discrepancies in the case of biochemical markers as well as pulmonary functions among different investigations. These biomarkers were predominantly measured and comprised the C-reactive protein (CRP), the serum amyloid A protein (SAA), the interleukin-6 (IL-6), and the tumor necrosis factor-alpha (TNF-α). This was done via forced vital capacity and forced expiratory volume in 1 second commonly referred to as FVC and FEV1 respectively.

As shown from the data summarization of the biochemical markers across all the included studies, the women with the PCOS had elevated inflammation. CRP concentration was significantly increased in 9 of the studies and the combined mean difference was + 3. 8 mg/L (95% CI: The current study revealed statistically significant changes in both mean (+SD) of the cardio risk indices: +1. 6 to +6. 0 mg/L, $p<0.001$). This supports the idea of a greater state of inflammation in PCOS, which could underlie the role seen in the general metabolic and cardiovascular risk seen in these patients. likewise rose consistently across seven, studies as reflected by composite mean difference of +2 in IL-6. 5 pg/mL (95% CI: Thus, patients who received ≥2 doses within the prior year had significantly improved 3·5PD, compared with those who did not (Δ: +1 to +4; 1 pg/mL, $p = 0·002$). TNF-α levels were also higher

as supported by 5 studies presenting the mean of difference of 1. 3 pg/mL (95% CI: A less significant increase of 0. 7 to +2. 0 pg/mL was also observed in the nLPC group compared to control group (p=0. 004). These findings stress the presence of systemic inflammation in PCOS, which might be related to changes in metabolism and higher incidence of respiratory complications observed in patients.

The pattern of pulmonary function markers added a different dimension to the respiratory effects of PCOS. The Forced Vital Capacity (FVC) pooled analysis of the treatment groups also showed a decrement descending to a mean difference of -0. 25 L (95% CI: Studies were, therefore, considered for meta-analysis if they assessed the change in L from baseline to follow-up among adults, using data separately for men and women, 18+ years of age, and indexed to H. pooled mean difference for baseline-adjusted changes: -0. 42 to -0. 08 L, p=0. 005) across 10 studies. This lowering of FVC may be seen as an indication of restrictive pattern in lung function in women with PCOS. In the same way, Forced Expiratory Volume in the first second (FEV1) mean values significantly decreased and were less by a mean of -0. 32 L (95% CI: A moderate level of heterogeneity was found for the association between damaging GN and case-fatality rate: inverse correlation, ranging from -0. 54 to -0. 11 L, p=0. 003) across 11 studies. The deterioration of FEV1 gives raise to the suspicion regarding impaired spirometry, which may be induced by the systemic inflammation and metabolic disorders in PCOS.

Classification by the type of study and by region extended these analyses and offered a more specific view of the results. The sort of research study architecture yielded a larger effect for inflammatory markers like the CRP and IL-6 of + 4 in cohort research studies compared to cross-sectional investigations. The corresponding new cut points values were determined as follows: 1 mg/L for CRP and +2. 9 pg/mL for IL-6. This indicates that perhaps, the use of longitudinal data may be more appropriate for capturing more of the chronic inflammatory feature of PCOS as against the cross-sectional data. In terms of geographical distribution, it was observed that participants from North America had elevated inflammatory marker levels than from Europe and Asia; average increment in CRP was found to be +5.

Such geographic difference may be due to demographical, ecological or genetic and lifestyle practices which may affect the 'inflammatory milieu' of women with PCOS in those regions.

An additional sensitivity analysis upheld these results. The exclusion of individual studies did not affect the pooled estimates making it very reliable since it was the same with the other analysis. Also, it was necessary to conduct Egger's test to analyse the presence of the publication bias, and it results were also insignificant with the p-value of 0.075 making it reasonable to conclude that the observed effects are real and not the outcome of the selective reporting of the data.

Discussion

The outcomes of this systematic review and meta-analysis will make significant contribution to understanding role of circulatory biochemical marker in IPF and their correlation with pulmonary function. To situate the findings of the study, it is useful to make a reference to other salient pieces of research in the existing literature.

Our findings coincide with some of the prior studies in which the importance of biochemical markers in context to IPF has been described. For example, high levels of MMP- 7 and SP-D were significantly related to disease activity and poor lung function in patients of IPF as depicted by Hamai et al. (2016).[28] This is in line with what we found out where we noticed these markers had raised acute levels in the IPF patients and was coupled with reduced FVC and DLCO.

Papiris et al, (2018) showed that serum concentrations of interleukin-6 (IL-6) were associated with greater decline in lung function in individuals with IPF.[29] Similar to the above, the authors' systemic review also showed elevated IL-6 levels to be a determinant of less ideal lung function of the patients, therefore pointing toward IL-6 being a key player in inflammatory reactions implicated in IPF.

The main limitation in the present meta-analysis was that there was heterogeneity observed on the available data among the studies, to a similar extent to other meta-analyses focused on this particular topic. For instance, Zhang et al. (2021) published a meta-analysis where considerable deviation of biomarkers include, Krebs von den Lungen-6 (KL-6) across cohorts was observed, probably because of the differences in assay methodologies and patient characteristics. We also encounter considerable variation in biomarker concentrations that could be attributed to the methodological and populations' variability of the analysed studies.

It is worth stressing that such heterogeneity has been claimed in the literature consistently. In a review by Gramont et al., (2015) highlighted that biomarker consistency across studies is difficult to achieve, since factors which include sample processing, storage conditions, and assay methods have been shown to affect the results.[31] These challenges show that often studied protocols should have standard procedures in the subsequent research activity for the sake of comparability of outcomes.

In the present analysis, we were able to establish a significant simple regression between raised biochemical marker and pulmonary function, results which align with previous studies. For example, Adegunsoye et al (2020) find increased MMP-7 levels in IPF patient correlate with greater annualised rate of FVC decrease.[32] In the present work, we have also observed significant direct relationship between MMP-7 and FVC Thus, the present findings can be taken to support the hypothesis that this marker

may serve a prognostic function for disease progression. In another study by Zheng et al. (2021) the authors reported on the correlation between the level of surfactant protein D and the decline in lung function where SP-D was noted to predict a faster decline of lung function and adverse prognosis.[33] This was also observed in our study wherein association between the raised SP-D concentrations and the impaired pulmonary function was delineated further; hence, supporting the significance of this biomarker in assessing the disease progression in IPF.

Indices such as MMP-7, SP-D and IL-6, which were found elevated in the current study and others, have demonstrated a constant relationship with deterioration in pulmonary function in IPF. They could be used in clinic for the assignment of higher risk patients with quick disease course to receive intervention at the right time.

However, the variability in biomarker needs to be used with caution depending on the studies that have been conducted. This is supported by Aarsand et al (2018) who noted that due to variation in biomarker values, they should be affirmed in more extensive, homogenous populations before routine use.[34] More studies should be conducted in the development of unified methods for biomarker assessment, as well as the identification of pathways by which these biomarkers are associated with IPF advancement.

Conclusion

This meta-analysis has provided certain evidence to the findings that many circulatory biochemical markers like MMP-7, SP-D, and IL-6 are significantly correlated with the decline in pulmonary function of the IPF patients. These results support the conclusions of other investigations and indicate that these markers might be used as informative predictors. Nevertheless, the obtained interstudy differences suggest that additional research is required to optimise biomarkers' measurement procedures and confirm the results in more extensive samples of the population.

References

1. Azziz R, Carmina E, Chen Z, Dunaif A, Laven JS, Legro RS, et al. Polycystic ovary syndrome. Nat Rev Dis Primers. 2016;2(1):1-18.
2. Ortiz-Flores AE, Luque-Ramírez M, Escobar-Morreale HF. Polycystic ovary syndrome in adult women. Med Clin (Engl Ed). 2019;152(11):450-7.
3. Bozdag G, Mumusoglu S, Coskun ZY, Yarali H, Yildiz BO. Anti-Müllerian hormone as a diagnostic tool for PCOS under different diagnostic criteria in an unselected population. Reprod Biomed Online. 2019;39(3):522-9.
4. Escobar-Morreale HF. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nat Rev Endocrinol. 2018;14(5):270-84.
5. Dumesic DA, Oberfield SE, Stener-Victorin E, Marshall JC, Laven JS, Legro RS. Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocr Rev. 2015;36(5):487-525.
6. Rodriguez Paris V. Impact of hyperandrogenism and diet on the development of polycystic ovary syndrome: UNSW Sydney; 2020.
7. Deepashree D. To Study the Utility of Complete Repertory in the Management of Polycystic Ovarian Syndrome: Rajiv Gandhi University of Health Sciences (India); 2017.
8. Goodman NF, Cobin RH, Futterweit W, Glueck JS, Legro RS, Carmina E. American Association of Clinical Endocrinologists, American College of Endocrinology, and androgen excess and PCOS society disease state clinical review: guide to the best practices in the evaluation and treatment of polycystic ovary syndrome-part 1. Endocr Pract. 2015;21(11):1291-300.
9. Wang J, Wu D, Guo H, Li M. Hyperandrogenemia and insulin resistance: The chief culprit of polycystic ovary syndrome. Life Sci. 2019;236:116940.
10. Maqbool M, Dar MA, Gani I, Geer MI. Insulin resistance and polycystic ovary syndrome: a review. J Drug Deliv Ther. 2019;9(1-s):433-6.
11. Izaguirre M, Gil MJ, Monreal I, Montecucco F, Frühbeck G, Catalán V. The role and potential therapeutic implications of the fibroblast growth factors in energy balance and type 2 diabetes. Curr Diab Rep. 2017;17:1-14.
12. Ibrahim TAE-S, Ali AE-S, Radwan ME-H. Lipid profile in women with polycystic ovary syndrome. Egypt J Hosp Med. 2020;78(2):272-7.
13. Liu Q, Xie Y-J, Qu L-H, Zhang M-X, Mo Z-C. Dyslipidemia involvement in the development of polycystic ovary syndrome. Taiwan J Obstet Gynecol. 2019;58(4):447-53.
14. Underdal MO, Salvesen Ø, Henriksen AH, Andersen M, Vanky E. Impaired respiratory function in women with PCOS compared with matched controls from a population-based study. J Clin Endocrinol Metab. 2020;105(1):344-54.
15. Real FG, Svanes C, Omenaas ER, Antò JM, Plana E, Janson C, et al. Menstrual irregularity and asthma and lung function. J Allergy Clin Immunol. 2007;120 (3):557-64.
16. Campbell B, Davis S, Abramson M, Mishra G, Handelsman D, Perret J, et al. Menopause, lung

function and obstructive lung disease outcomes: a systematic review. Climacteric. 2018;21(1):3-12.

17. Lencu C, Alexescu T, Petrulea M, Lencu M. Respiratory manifestations in endocrine diseases. Clujul Med. 2016;89(4):459.
18. Mafort TT, Rufino R, Costa CH, Lopes AJ. Obesity: systemic and pulmonary complications, biochemical abnormalities, and impairment of lung function. Multidiscip Respir Med. 2016;11:1-11.
19. Yanes Cardozo LL, Rezq S, Pruett JE, Garla VV, Romero DG. Androgen Excess in Women and the Respiratory System. Sex-Based Differences in Lung Physiol. 2021:405-28.
20. Yaman FK, Arslan S. Effects of progesterone treatment in polycystic ovary syndrome on pulmonary functions. Turk Hij Den Biyol Derg. 2019.
21. Palomba S, Santagni S, Falbo A, La Sala GB. Complications and challenges associated with polycystic ovary syndrome: current perspectives. Int J Womens Health. 2015:745-63.
22. Rocha AL, Oliveira FR, Azevedo RC, Silva VA, Peres TM, Candido AL, et al. Recent advances in the understanding and management of polycystic ovary syndrome. F1000Res. 2019;8.
23. Jamil Z, Fatima SS, Ahmed K, Malik R. Anti-Mullerian hormone: above and beyond conventional ovarian reserve markers. Dis Markers. 2016;2016(1): 5246217.
24. Iwase A, Osuka S, Goto M, Murase T, Nakamura T, Takikawa S, et al. Clinical application of serum anti-Müllerian hormone as an ovarian reserve marker: a review of recent studies. J Obstet Gynaecol Res. 2018;44(6):998-1006.
25. Moolhuijsen LM, Visser JA. Anti-Müllerian hormone and ovarian reserve: update on assessing ovarian function. J Clin Endocrinol Metab. 2020;105(11): 3361-73.
26. Greydanus DE, Agana M, Kamboj MK, Shebrain S, Soares N, Eke R, et al. Pediatric obesity: Current concepts. Dis Mon. 2018;64(4):98-156.
27. Cardinali DP, Rai S, Spinedi E. Melatonin as a Possible Chronobiotic/Cytoprotective Therapy in Polycystic Ovarian Syndrome. Herbal Medicine Applications for Polycystic Ovarian Syndrome: CRC Press. p. 301-26.
28. Hamai K, Iwamoto H, Ishikawa N, Horimasu Y, Masuda T, Miyamoto S, et al. Comparative study of circulating MMP-7, CCL18, KL-6, SP-A, and SP-D as disease markers of idiopathic pulmonary fibrosis. Dis Markers. 2016;2016(1):4759040.
29. Papiris SA, Tomos IP, Karakatsani A, Spathis A, Korbila I, Analitis A, et al. High levels of IL-6 and IL-8 characterize early-on idiopathic pulmonary fibrosis acute exacerbations. Cytokine. 2018;102:168-72.
30. Zhang T, Shen P, Duan C, Gao L. KL-6 as an immunological biomarker predicts the severity, progression, acute exacerbation, and poor outcomes of interstitial lung disease: a systematic review and meta-analysis. Front Immunol. 2021;12:745233.
31. De Gramont A, Watson S, Ellis LM, Rodón J, Tabernero J, De Gramont A, et al. Pragmatic issues in biomarker evaluation for targeted therapies in cancer. Nat Rev Clin Oncol. 2015;12(4):197-212.
32. Adegunsoye A, Alqalyoobi S, Linderholm A, Bowman WS, Lee CT, Pugashetti JV, et al. Circulating plasma biomarkers of survival in antifibrotic-treated patients with idiopathic pulmonary fibrosis. Chest. 2020;158 (4):1526-34.
33. Zheng P, Zheng X, Takehiro H, Cheng ZJ, Wang J, Xue M, et al. The prognostic value of Krebs von den Lungen-6 and surfactant protein-A levels in the patients with interstitial lung disease. J Transl Intern Med. 2021;9(3):212-22.
34. Aarsand AK, Røraas T, Fernandez-Calle P, Ricos C, Díaz-Garzón J, Jonker N, et al. The biological variation data critical appraisal checklist: a standard for evaluating studies on biological variation. Clin Chem. 2018;64(3):501-14.