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#### The analysis of the causes of PCOS (*Polycystic Ovary Syndrome*)

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#### **ABSTRACT**

Introduction. PCOS (Polycystic Ovary Syndrome) is an ovulation disorder that causes infertility in women of childbearing age. As many as 4-18% of them have PCOS which causes 5-10% of women of childbearing age to become infertile. The purpose of this literature review is to explain and analyze the factors that cause the incidence of PCOS based on empirical studies of the last five years. Method. This type of research is a literature review with a research design using the PRISMA approach. The search was conducted in five electronic databases (Google Scholar, PubMed, Willey, Cochrane, Elsevier and ProQuest) published in the last five years, from 2015- 2020 published in English and according to keywords. In the journal search, 4496 articles were found, then duplication was selected, the inclusion and exclusion criteria were eligible, and the full text was left, leaving 12 articles. Result. General characteristics in study selection were obtained mostly from PubMed (75%). The study design was almost partially Cross-Sectional (41.6%). Most (33.3%) years of publication were 2016 and 2018 and most (100%) journals were English. While the factors causing PCOS such as hyperinsulinemia/insulin resistance (n=7), obesity (n=5), and hyperandrogenism factors (n=3). Analysis. The results of this review state that hyperinsulinemia/insulin resistance, obesity, and hyperandrogenism can cause the incidence of PCOS. Discussion. Further research is needed on the factors that influence the incidence of PCOS.

Keywords: factors, PCOS, polycystic ovary syndrome.

#### INTRODUCTION

Infertility is the inability to produce offspring. Infertility cases that occur in women occur in 40% -50% of cases while men are 30% and other causes are about 20% -30% of couples1 (Henriyanita, 2019). In 1990 the incidence of infertility reached 42 million and increased in 2010 as many as 48.5 million cases<sup>2,3</sup>. According to WHO (World Health Organization) the incidence of Infertility cases are increasing every year<sup>4</sup>. The cause of infertility in men is easier to know by checking their sperm. In women, it is necessary to examine the eggs and the number of eggs produced, to check the fallopian tubes, the condition of the uterus, the ability of the cervix to distribute sperm cells, and ovulation disorders or PCOS (Polycystic Ovary Syndrome)<sup>1</sup>. Syndrome is caused by hyperandrogenemia (HA), hyperinsulinemia/insulin resistance (IR), hormonal imbalance, cardiovascular disease, obesity, and other health problems<sup>4</sup>. PCOS develops when the ovaries are stimulated to produce too many androgens, especially testosterone, which releases large amounts of the hormone LH in the anterior pituitary gland<sup>7</sup>. Increased growth factors cause an increase in ovarian response to Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH), so that ovarian follicle development increases and androgen production also increases. Excessive follicle development will have an impact on the number of cystic follicles. There is a relationship between obesity and an increased risk of polycystic ovaries, from increased insulin resistance which causes theca cells to produce androgens and inhibits Sex Hormone Binding Globulin (SHBG) so that free androgens increase. This causes many androgens to be aromatized into estrogen which then produces LH and triggers follicular maturation<sup>6</sup>. The prevalence of PCOS varies widely from 2.2% to 26% globally. In some Asian countries, prevalence rates range from 2% to 7.5% in China and 6.3% in Sri Lanka<sup>7</sup>. A total of 8,612 women between the ages of 28-33 years, 5.8% of them experienced PCOS and 309 or 72% of women with PCOS experienced infertility8. In dealing with PCOS, pharmacological therapies can be used, including ovulatory dysfunction-related infertility (clomiphene citrate, aromatase inhibitors, and glucocorticoids, metformin), menstrual cycle disorders (cyclic progestins and combined oral contraceptives such as estrogen and progestins), androgen related symptoms (anti-androgens). glucocorticoids, gonadotropin-releasing hormone agonists, oral contraceptives such as ethinyl estradiol) and vitamin D therapy<sup>9,21</sup>.

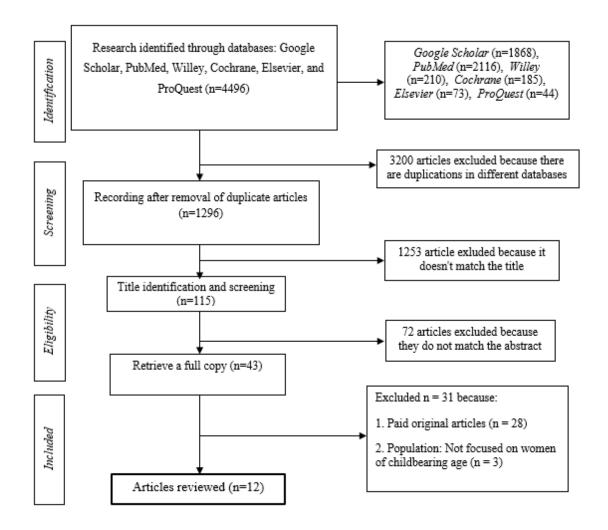
#### **METHODS**

The method used in this research is Literature Review. This Rivew literature shows the relationship between writing and research statements that have been formulated. The protocol and evaluation of the literature review will use the PRISMA Checklist to determine the selection of studies that have been found and adapted to the objectives of the literature review. The purpose of this literature is to provide a complete and structured summary of previous research using secondary data. In the initial step, 4496 articles were obtained from 2015-2020 with the

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keywords: factors, polycystic ovary syndrome, women of childbearing age, causes of PCOS in women, factors of polycystic ovary syndrome in women, analysis of factors for PCOS reproductive aged women. This research was conducted using 5 databases, namely Google Scholar, PubMed, Willey, Cochrane, Elsevier,



#### **RESULTS**

		RESULIS		
No	Judul, Author, Tahun, Volume	Metode (Desain, Sampel, Variabel, Instrumen, Analisis)	Hasil Penelitian	Database
1	Inter-related effects of insulin resistance, hyperandrogenism, sympathetic dysfunction and chronic inflammation in PCOS  Article type: 3 Original Article-Australia, Japan, SE Asia doi: 10.1111 / cen.13808  https://onlinelibrary.wiley.com/doi/abs/10.1111/cen. 13808  Tahun 2018	D: Cross sectional S: 49 women with PCOS and 23 controls total 72 V: insulin resistance, hyperandrogenism, sympathetic dysfunction and chronic inflammation I: community data A: Pearson test	Testosterone stages had been most importantly related to PCOS, after adjustment for age and BMI. In women with PCOS, testosterone and FAI had been each good sized with insulin resistance in PCOS women.	PubMed
2	Association between Insulin Resistance and Cardiovascular Risk Factors in Polycystic Ovary Syndrome Patients  Rev Bras Ginecol Obstet Vol. 40 No. 4/2018  DOI https://doi.org/ 10.1055/s-0038-1642634. ISSN 0100-7203.  https://pubmed.ncbi.nlm.nih.gov/29747212/  Tahun 2018	D: Cross sectional S: 83 PCOS patients V: age, weight, height, Ferriman-Gallwey score, body mass index, waist circumference, systolic, diastolic, cholesterol, high density lipoprotein, low density lipoprotein, Non-HDL lipoprotein, triglycerides, glucose (fasting) I: medical record A: Proportion test, Chisquare test, and Fisher's exact test	IR turned into statistically better in overweight women and consequently extra susceptible to growing PCOS than women with everyday BMI. No affiliation turned into discovered among IR and WC, BMI, LAP.	PubMed
3	Polycystic Ovary Morphology Is Associated with Insulin Resistance in Women with Polycystic Ovary Syndrome  DR SO-HYEON HONG (Orcid ID: 0000-0001-5194-8924). Article type: 3 Original Article - Australia, Japan, SE Asia  doi: 10.1111/cen.13380  https://pubmed.ncbi.nlm.nih.gov/28543550/#:~:text =Results%3A%20Polycystic%20ovary%20morphol ogy%20was,01).  Tahun 2017	D: Cross sectional S: 679 women with PCOS and 272 control women, a total of 951 V: glucose and insulin levels, testosterone levels, ovarian volume, and follicle number I: medical record A: Multiple regression	PCOS women had drastically better overall testosterone stages and decrease wide variety of menstrual durations according to 12 months and ovarian follicle rely related to IR in women with PCOS after adjusting for age, BMI, and overall testosterone.	PubMed
4	Association of leptin and insulin resistance in PCOS: a case-controlled study  Int J Reprod BioMed Vol. 15. No. 7. pp: 423-428, July 2017  https://pubmed.ncbi.nlm.nih.gov/29177243/  Tahun 2017	D: Case control S: 378 women V: Serum leptin, body mass index (BMI), several hormones, I: medical record A: Pearson's test	Leptin degrees had been substantially correlated with frame weight and BMI in women, suggest FSH degrees had been substantially decrease in PCOS patients, LH and testosterone degrees had been generally better in PCOS women.	PubMed
5	Insulin resistance and obesity among infertile women with different polycystic ovary syndrome phenotypes  Scientific RepoRts   7: 5339   DOI:10.1038/s41598-017-05717-y  https://www.nature.com/articles/s41598-017-05717-y  Tahun 2017	D: Cross sectional S: 213 women V: age, age of menarche, IR I: database A: Chi-square tests, ANOVA, t-test	No relationship was observed between BMI and waist circumference, women had a significant phenotype of PCOS with insulin resistance, and age and menstrual age were not significant for PCOS.	Proquest

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6	Insulin resistance and oxidative marker in women with PCOS  ARCHIVES OF PHYSIOLOGY AND BIOCHEMISTRY  DOI: 10.1080/13813455.2018.  1499120  https://pubmed.ncbi.nlm.nih.gov/30450993/#;~:text =Conclusion%3A%20Our%20study%20suggests%2 0that.grade%20inflammation%20and%20cardiovasc ular%20diseases.  Tahun 2018	D: case control study S: 200 women V: BMI, insulin levels, PCOS I: measurement of weight and TB then calculate BMI, measurement of glucose levels in fasting and non-fasting conditions A: t-test, Kruskal-Wallis test	Fasting blood glucose, serum insulin, and IR are elevated in overweight and non-obese women with PCOS; Obese women with PCOS have an increased risk of moderate inflammatory and cardiovascular diseases.	PubMed
7	A case–control observational study of insulin resistance and metabolic syndrome among the four phenotypes of polycystic ovary syndrome based on Rotterdam criteria  Jamil et al. Reproductive Health 2015, 12:7 http://www.reproductive-health-journal.com/content/12/1/7	D : Case control S : 526 women V : IR, Oligo-anovulation, Hyperandrogenism I: medical record A : t-test, post-hoc test	In women with oligoanovulation (O) and PCO (P) morphology, levels were significantly lower than in women with OP and HA phenotypes. BMI, waist circumference, triglycerides (cardiovascular risk), HOMAIR, and type 2 diabetes are associated with an increased risk of metabolic disorders.	PubMed
8	Overweight and obese but not normal weight women with PCOS are at increased risk of Type 2 diabetes mellitus a prospective, population-based cohort study  Human Reproduction, pp. 1–9, 2016 doi:10.1093/humrep/dew329  https://pubmed.ncbi.nlm.nih.gov/28031324  Tahun 2016	D: cohort study S: 1836 women V: PCOS, obesity, overweight I: questionnaire A: t-test, Mann–Whitney U-test	Polycystic ovary syndrome significantly increases the risk of DMT2 in obese and overweight women; Normal weight women with PCOS are not at increased risk of prediabetes or type 2 diabetes.	Google schoolar
9	Relationship between hyperandrogenism, obesity, inflammation and polycystic ovary syndrome  Asli Nehir Aytan, Ercan Bastu, Irem Demiral, Huri Bulut, Murat Dogan & Faruk Buyru (2016):  Gynecological Endocrinology,  DOI:10.3109/09513590.2016.1155208  https://pubmed.ncbi.nlm.nih.gov/26 951881/#:~:textBody%20mass%20index%20had% 20a,the%20inflammatory%20status %20and%20hyperandrogenism.	D: prospective study S: 88 women V: hyperandrogenism, obesity, inflammation and polycystic ovary syndrome I: medical record A: t test, ANOVA	FAI values were significantly higher in PCOS patients, inflammation and hyperandrogenism increased in obese PCOS patients, weight gain in women with a genetic predisposition to PCOS.	PubMed
10	Tahun 2016 Association of obesity and overweight with the prevalence of insulin resistance, pre-diabetes and clinical biochemical characteristics among infertile Mexican women with polycystic ovary syndrome BMJ Open 2016;6:e012107. doi:10.1136/bmjopen-2016-012107 https://bmjopen.bmj.com/content/6/7/e012107 Tahun 2016	D: Cross sectional S: 20,906 women V: infertile with PCOS diagnosis, normal weight (body mass index (BMI) (18.5 - 24.9), overweight (BMI 25 - 29.9), and obesity (BMI 30) I: medical record A: Kruskal-Wallis test, Fisher's exact test	Infertile women with PCOS who are obese or overweight are dominated by IR and prediabetes.	PubMed
11	Vitamin D in polycystic ovary syndrome: Relationship to obesity and insulin resistance DOI 10.1002/mnfr.201500259 Mol. Nutr. Food Res. 2016, 60, 110–118	D : Cross sectional S : 76 women V : PCOS, obesity, IR, vitamin D	Vitamin D levels were lower in obese women with PCOS than in overweight controls, and vitamin D was associated with IR in the PCOS group.	PubMed

	https://pubmed.ncbi.nlm.nih.gov/26255991/  Tahun 2016	I: medical record  A: linear multivariate analysis		
12	Close correlation between hyperandrogenism and insulin resistance in women with polycystic ovary syndrome-Basedmon liquid chromatography with tandem mass spectrometry measurements  J Clin Lab Anal. 2018;e22699  DOI: 10.1002/jcla.22699  https://onlinelibrary.wiley.com/doi/epdf/10.1002/jcl a.22699  Tahun 2018	D: cohort study S: 671 women V: hyperandrogenism, insulin resistance, PCOS I: medical record A: Kolmogorov- Smirnov test, chi square, ANOVA	Higher IR and risk of HA elevation among PCOS women	Wiley

#### DISCUSSION

The 12 related articles, then analyze the factors that cause PCOS (Polycystic Ovary Syndrome). These factors were found to be hyperinsulinemia/insulin resistance, obesity, and hyperandrogen. There are 7 articles that have been reviewed in which hyperinsulinemia/insulin resistance is the cause of PCOS. This result is in line with the opinion of several researchers, which states that respondents who have hyperinsulinemia/insulin resistance cause PCOS<sup>10</sup>. Insulin resistance affects the ovulatory cycle of women of reproductive age. Insulin resistance can cause insulin levels to rise in the blood (hyperinsulinemia). In a study conducted by Wanderley (2018), 50-80% of PCOS women with hyperinsulinemia/insulin resistance experienced menstrual cycle disturbances of more than 35 days (55.43%), women who experienced amenorrhea (40.96%), and most PCOS patients suffer from this condition with the severity of PCOS related to the IR condition<sup>12</sup>. According to other research that women with PCOS are overweight and have high fasting glucose and insulin levels and higher total testosterone levels and the number of menstruations is less frequent during the year this affects the number of ovarian follicles associated with IR in women with PCOS<sup>13,14</sup>. Al-Jefout's research showed that 133 or 83.6% of PCOS women experienced insulin resistance in 159 samples and showed a high FAI (Free Androgen Index), namely abnormal testosterone levels in PCOS women's bodies<sup>15</sup>. According to research (Jamil et al., 2015) high insulin resistance is found in women with PCOS which can cause Metabolic Syndrome, namely hyperinsulinemia and hyperandrogens<sup>16</sup>. Research conducted by (Joham et al., 2016) BMI and IR are positively related to serum leptin in infertile PCOS women, in the PCOS group, 9 out of 99 women were obese with a BMI 30 and 31 women were overweight with 25≤ BMI  $29.9^{17}$ .

There are 5 articles discussed about obesity factors, it was found that respondents who were obese were the cause of PCOS. The results of the study are in line with several researchers, according to Al-Jefout (2017) measurement of BMI in the obesity category of 39.9% and waist circumference in the obese category of 25.9% in the study experiencing insulin resistance and hyperandrogen, which causes hirutism symptoms. According to Ollila's research (2017), it shows that the risk of T2DM in women with PCOS is mainly due to being overweight/obese and normal weight women with PCOS do not experience an increased risk<sup>18</sup>. According to research by Nehir Aytan (2016) obese PCOS women have higher androgen levels than lean PCOS women<sup>19</sup>. According to research by Reyes-Muñoz (2016), it was found that obese women found high glucose and insulin hormone levels which had an impact on increasing FAI (Free Androgen Index)<sup>20</sup>. Research conducted by Joham (2016) low vitamin D levels in women with PCOS with obesity around 27-56%<sup>21</sup>.

There are 3 articles that discuss hyperandrogen factors, all of which state that hyperandrogen factors affect the incidence of PCOS. These results are in line with the other studies in women with PCOS who are obese with low FSH hormones, increased LH, and increased FAI due to impaired production of Sex hormone binding globulin (SHGB) in the liver<sup>10,19</sup>. Research conducted by Yang (2019) that women with PCOS experienced hyperandrogen as much as 80.99%, IR with HA was strongly associated in this case because FAI levels increased<sup>14</sup>.

#### **CONCLUSION**

The results of this review reported 7 out of 12 journals discussing the PCOS incident factor, namely hyperinsulinemia/insulin resistance, the review results reported 5 out of 12 journals discussing the PCOS incident factor, namely obesity, and the review results reported 3 out of 12 journals discussing the PCOS incident factor, namely hyperandrogen.

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