Internal and External Data Needs Regarding Effective Treament for Insulin Resistance in PCOS Patients

Cassidy Freeman

University of Mary

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Professor Lauren Terzo

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Polycystic Ovarian Syndrome or PCOS is defined as a set of symptoms relating to a hormonal imbalance affecting women and girls of reproductive age (National Institute of Child Health and Human Development, 2022). To be diagnosed with PCOS, patients must have 2 of the 3 diagnostic conditions. These conditions include absence of ovulation, high levels of androgens or signs of high androgens, and abnormal growths on one or both ovaries. According to the NICHD (2022), women with PCOS are at a higher risk of obstructive sleep apnea, insulin resistance, metabolic syndrome, type 2 diabetes, obesity, heart disease, mood disorders, and endometrial hyperplasia.

PCOS affects between 6-10% of pre-menopausal women (Barber et al., 2015). Of these women that have PCOS, it has been estimated that 50-90% have insulin resistance. Weight gain and obesity in the development of PCOS is mediated by the worsening of insulin resistance. It has been found that weight loss of 5% body weight has improved insulin sensitivity. The role of insulin resistance in the pathogenesis of PCO is supported by observations that improve insulin resistance through weight loss or drug therapy (Barber et al., 2015).

People typically do not realize they are insulin resistant until their doctor completes a physical exam or conducts routine blood work. Clinical manifestations of insulin resistance include acanthosis nigricans, skin tags, alopecia, amenorrhea, hirsutism, virilization, and infertility in females (Mantzoros, 2022). Treating insulin resistance is important because it can lead to type 2 diabetes, coronary artery disease, metabolic syndrome, nonalcoholic fatty liver disease, and certain cancers like endometrial cancer (Mantzoros, 2022).

To help with insulin resistance, healthcare providers prescribe a medication called metformin. Recently, studies have shown that glucagon-like peptide 1 receptor agonists, like semaglutide, improve insulin resistance while also reducing weight in women with PCOS (Ma et al., 2021). Metformin is able to decrease androgen levels, increase ovulation rate, and improve glucose tolerance in patients with PCOS. The purpose of this paper is to provide the internal data needs for the following PICO question, identify quality external data, and review the data that was found and examine how it is related to the PICO question.

PICO Question

For premenopausal women with Polycystic Ovarian Syndrome, does the use of Semaglutide compared to Metformin improve symptoms of insulin resistance?

Internal Data

Table 1

Internal Data

Data Need	Special considerations	Source
# of patients with polycystic ovarian syndrome	Consider when these patients were diagnosed	Electronic Health Record
# of patients with PCOS receiving Semaglutide	Consider if they tried Metformin prior to using Semaglutide	Electronic Health Record
# of patients with PCOS receiving Metformin	Consider side effects these patients are having	Electronic Health Record
Blood glucose levels for patients receiving Semaglutide	Consider other comorbidities that may cause altered blood glucose levels	Electronic Health Record

Blood glucose levels for patients receiving Metformin	Consider other comorbidities that may cause altered blood glucose levels	Electronic Health Record
Lipid levels for patients receiving Semaglutide	Consider other factors causing altered lipid levels	Electronic Health Record
Lipid levels for patients receiving Metformin	Consider other factors causing altered lipid levels	Electronic Health Record
Subjective symptoms for PCOS patients	Consider a list of symptoms for patients to choose from	Electronic Health Record
Number of PCOS patients on semaglutide with A1C less than 5.6	Consider other factors such as diet or comorbidities that may affect A1C levels	Electronic Health Record
Number of PCOS patients on Metformin with A1C less than 5.6	Consider other factors such as diet or comorbidities that may affect A1C levels	Electronic Health Record
# of patients reporting weight loss on semaglutide	Consider if they were trying to lose weight using other methods	Electronic Health Record
# of patients reports weight loss on Metformin	Consider if they were trying to lose weight using other methods or if they had side effects that disrupted their intake	Electronic Health Record

External Data

When conducting a search to acquire external evidence relative to the presented PICO question on the effects of treatment options for premenopausal women with PCOS, several research databases are available for consideration. A search for quality external data was

conducted through CINHAL, MEDLINE, and Cochrane databases. Developing a search strategy is imperative to accumulate the best available evidence to support a proposed PICO question. Strategies to find the best evidence in research includes using keywords provided in the PICO question (Melnyk & Fineout-Overholt, 2018). An initial search was done using keywords provided in the PICO question. Keywords utilized to search CINHAL, MEDLINE, and Cochrane were insulin resistance of PCOS women, semaglutide and PCOS, metformin and PCOS, and PCOS treatment.

Searching keywords or phrases individually can generate many research articles. To narrow your search, linking together keywords and phrases using a Boolean connector such as AND, it allows for only articles containing the combined keywords and phrases (Melnyk & Fineout-Overholt, 2018). Searching keywords in various combinations through the Boolean connecter AND, allowed for the narrowing of articles pertinent to the PICO question. See Table 2 for the number of results these keywords and combinations generated per database.

Utilizing additional limitations and filters to the search terms listed in Table 2 reduced the number of articles even more. Filters placed on the keywords and their combinations were to contain articles published in the last five years and academic journals. Five quality articles that are pertinent to the PICO question were found after conducting a search with appropriate keywords, connecting keywords with the Boolean connector AND, and applying the previously listed filters. These five articles and the key information presented in them are detailed in Table 3.

Table 2

External Data

	CINHAL	MEDLINE	Cochrane

Insulin Resistance in PCOS	188	1,175	1
Semaglutide	457	1,091	0
Metformin	9,644	28,950	52
PCOS Treatment	493	2,248	10
1 and 2	373	1,008	0
1 and 3	28	177	1
2 and 4	201	689	0
3 and 4	125	574	4

Table 3

Matrix Grid

Full APA Reference Citation	Research Purpose	Study Design	Sample (Setting)	Data Collection/ Measures	Analysis/ Outcomes	Strengths/ Limitations	Joanna Briggs Level of Evidence	Study Quality
Ma, R., Ding, X., Wang, Y., Deng, Y., & Sun, A. (2021). The therapeutic effects of glucagon-like agonists and metformin on polycystic ovary syndrome: A protocol for	To compare the effects between GLP-1 receptor agonists and metformin, and between GLP-1 receptor agonist-metformin combination and GLP-1 receptor	Systematic review and meta-analysis	7 studies were included in the meta-analysis with a total of 464 participants.	7 studies were included in this for analysis. 2 reviewers independently searched medical literature in PubMed, EMBASE, Web of Science, and Cochrane library from the beginning to March 2020. A search of reference	Descriptive statistics. The meta-analysis found GLP-1 RA were significantly associated with lower BMI MD −1.72; 95% CI −2.46 to −0.99; I^2 = 0%, P < .001) and HOMA-IR (SMD −0.37; 95% CI	It was noted that all studies were assessed as having some risk of bias. There was an uncertain risk of selection bias. Limitations included small total sample sizes and wide 95% CIs which reduced the overall	Level 1	Low quality

systematic review and meta-analysis. *Medicine, 100(23), e26295.* https://doi.org/10.1097/md.0000000000026295	agonists in overweight/obese women with PCOS on anthropometric, metabolic, reproductive outcomes.	lists of all eligible studies and previous reviews was done. Studies were accepted if consisted of the following: patient with a diagnosis of PCOS, GLP-1 receptor agonist alone or the combination of GLP-1 receptor agonist were applied to PCOS patients, comparison between GLP-1 RA and metformin, between GLP-1 RA combined with metformin and GLP-1 alone, changes in obesity, menstrual frequency, metabolic or endocrine parameters, and adverse effects and RCTs with	-0.60 to -0.15; $I^2 = 0\%$, $P = .001$) compared with metformin, however, there was no significant differences on MFR and TT.	quality of the evidence.

	results published in English.

Abdalla, M. A., Shah, N., Deshmukh, H., Sahebkar, A., Ostlundh, L., Al-Rifai, R. H., Atkin, S. L., & Sathyapalan, T. (2021). Impact of pharmacological interventions on insulin resistance in women with polycystic ovary syndrome: A systematic review and meta-analysis of randomized controlled trials. *Clinical Endocrinology, 96(3),* 371-394. https://doi.org/10.1111/cen.14623	The purpose of this study was to review the literature on the effect of different pharmacological interventions on insulin resistance in women with PCOS.	Systematic review and meta-analysis	58 RCTs were found eligible.	Two investigators independently searched PubMed, EMBASE, MEDLINE, Scopus, Cochrane Central Library, and Web of Science in April 2020 and was updated in March 2021. Searches of open grey, clinicaltrial.gov, and Open thesis repository was also done. Inclusion criteria included RCT, adult females aged 18 and over with a diagnosis of PCOS, reported pharmacological interventions compared to placebo or other pharmacological events, reported outcomes such as	Descriptive Statistics and tables. There were significant reductions in the fasting blood glucose with metformin versus placebo standardized mean difference [SMD]: −0.23; 95% confidence interval [CI]: −0.40, −0.06; $I^2 = 0$ %, low-grade evidence) and acarbose versus metformin (mean difference [MD]: −10.50 mg/dl; 95% CI: −15.76, −5.24; $I^2 = 0$ %,) A significant reduction in HOMA-IR was seen with exenatide versus metformin (MD: −0.34;	It was noted that there was a high level of performance bias. In 16 of the RCTs no clear PCOS diagnostic criteria were detailed and was a main limitation of the included RCTs. There was a lack of robust clinical trials assessing the different pharmacological interventions in the management of PCOS.	Level 1	Low Quality

		fasting blood glucose, fasting insulin, HOMA-IR, and HOMA-B. Exclusion criteria includes case studies and animal studies, adolescent females, postmenopausal women, and women without PCOS, nonpharmacological interventions, pharmacological interventions versus dietary interventions, and pharmacological interventions versus physical activities or surgery.	95% CI: −0.65, −0.03; $I^2 = 0$ %).

Lyu, X., Lyu, T., Wang, X., Zhu, H., Pan, H., Wang, L., Yang, H., & Gong, F. (2021). The antiobesity effect of glp-1 receptor agonists alone or in combination with metformin in overweight/obese women with polycystic ovary syndrome: A systematic review and meta-analysis. *International Journal of Endocrinology, 2021,* 1-11. https://doi.org/10.1155/2021/661669	To evaluate the antiobesity effects of GLP-1Ras either as monotherapy or combined with MET in comparison with MET alone in overweight/obese PCOS patients by using a method of systematic review and meta-analysis.	Systematic review and meta-analysis	8 studies were included in the meta-analysis	Two independent reviewers searched Medline, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and Scopus databases from the beginning to October 2020. Studies were included if the patients were overweight/obese premenopausal women diagnosed with PCOS, GLP-1 RAs were used alone or combined with MET were compared with MET alone without dosage limitations, and the primary outcome was weight loss.	Descriptive statistics. The results showed that GLP-1RAs alone or combined with MET was associated with a greater weight loss ($N = 318$, WMD = −2.61, 95% CI: −3.51 to −1.72, P ≤ 0.001, $I2$ = 77.5%), more obvious reduction of waist circumference ($N = 276$, WMD = −3.46, 95% CI: −4.36 to −2.56, P ≤ 0.001, $I2$ = 0.0%), and body mass index (BMI) ($N = 318$, WMD = −0.93, 95% CI: −1.60 to −0.26, P = 0.007, $I2$ = 84.9%) in overweight/obese PCOS patients when compared	There was no conflict of interest in this study. The sample size was small. There was also considerable heterogeneity. Another limitation is there was a potential publication bias in the meta-analysis of BMI reduction degree. Finally, there were different definitions in the studies of what overweight/obese is.	Level 1	Moderate Quality

					with MET alone.			
Han, Y., Li, Y., & He, B. (2019). Glp-1 receptor agonists versus metformin in pcos: A systematic review and meta-analysis. *Reproductive BioMedicine Online, 39*(2), 332-342. https://doi.org/10.1016/j.rbmo.2019.04.017	To compare the efficacy and safety of a GLP-1 receptor agonist with those of metformin in women with PCOS through a meta-analysis to provide evidence-based medical strategies for clinicians treating PCOS	Meta-analysis	8 studies were included in the meta-analysis with a total of 375 women.	Two authors independently screened the literature from PubMed, EMBASE, Cochrane Library, WanFang Database, and CNKI starting from inception until June 2018. All RCTs reporting the efficacy and safety of GLP-1 receptor agonsists compared with Metformin for PCOS were included. Studies not published in English or Chinese were excluded as well as studies without a control group or if GLP-1 receptor agonists and/or	Descriptive statistics. GLP-1 receptor agonists were found to be superior to metformin for improving insulin sensitivity and reducing BMI and abdominal girth of women with PCOS.	Strengths include no prior meta-analysis on these issues has been as large. Another strength is that GLP-1 agonists have not been compared with other drugs. Limitations include the difference in statistical evidence was at the edge or statistical significance. A larger sample size needs to be considered. There was also a potential selection bias.	Level 1	Moderate quality.

				metformin was combined with other treatments.				
Xing, C., Li, C., & He, B. (2020). Insulin sensitizers for improving the endocrine and metabolic profile in overweight women with pcos. *The journal of Clinical Endocrinology & Metabolism, 105*(9), 2950-2963. https://doi.org/10.1210/clinem/dgaa337	To evaluate the efficacy of insulin sensitizers on menstrual frequency, sex hormone, and metabolic parameters in overweight women with PCOS.	Systematic review and meta-analysis	14 studies were included in the meta-analysis with a total of 619 women.	Two investigators independently searched medical literature in PubMed, EMBASE, the Cochrane Library, WanFang Database, the WeiPu database, and China National Knowledge Infrastructure from the dates of establishment to September 2019. To be included the following inclusion criteria had to be met: women were diagnosed with PCOS aged 18-49 years, BMI of ≥25 kg/m, diagnosis of PCOS based on the Rotterdam European	Descriptive Statistics. For overweight women with PCOS, both metformin combined with GLP-1 receptor agonists and metformin combined with TZDs appear superior to monotherapy in improving hyperandrogenemia. Metformin combined with TZDs could be particularly effective in promoting recovery of menstruation. Metformin with a GLP-1 receptor agonist has the advantage of improving fasting	One strength is that this is the first NMA comparing efficacy and safety of both monotherapy and combinations of different insulin sensitizers in the management of overweight women with PCOS. All original studies utilized a RCT design which reduced recall and selection bias. Limitations include lack of previous studies with overweight women with PCOS and a high heterogeneit	Level 1	Moderate quality

	Society for Human Reproduction and Embryology/ American Society for Reproductive Medicine standard or the National Institute of Child Health and Human Development, RCT study design, and included at least one of the outcomes of menstrual frequency, sex hormone parameters, glucose metabolism parameters, and obesity-related parameters, comparisons between the relevant interventions and the intervention period was at least 12 weeks.	glucose when compared to GLP-1 receptor agonists alone.	y. Publication bias also exists. The dosing regimens were also not consistent among the studies.

Synthesis of Literature

According to the five critiqued studies, GLP-1 receptor agonists, like semaglutide are thought to be superior when compared to PCOS in regards to decreasing symptoms of insulin

resistance. A commonality within all the studies is that there is success in improving insulin sensitivity when individuals lose weight. Another common finding within the studies is the evidence cannot be utilized for common practice due to the quality of the articles they were reviewing. There needs to be more high-quality research done to assess the efficacy of a GLP-1 receptor agonist on women with PCOS (Han et al., 2019). GLP-1 receptor agonists have several physiological effects including improving insulin resistance, inhibiting appetite and food intake, and delaying gastric emptying which leads to weight loss. In the study conducted by Xing et al (2020)., it was found that metformin plus a GLP-1 receptor agonist was more effective than a GLP-1 receptor agonist alone. This is something that had not been researched or looked at in the other four articles. It was also found that GLP-1 receptor agonists alone or combined with metformin was superior when compared with metformin alone in terms of weight loss, reduction of waist circumference, and BMI (Lyu et al., 2021).

Conclusion

Developing a PICO question when addressing the need for change in practice is imperative. A well-designed question aids the researcher in identifying the internal data needs and can guide the search for pertinent, high-quality external data. Having a well thought out strategy for searching external data can produce the best available evidence for the researcher. This also allows for the researcher to avoid missing valuable evidence. A PICO question that is supported by valid internal and external evidence can guide the successful implementation of new evidence based practice.

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