v. 4, n. 87, 2024

International Journal of Health Science

POLYCYSTIC OVARY SYNDROME AS A RISK FACTOR FOR DEVELOPING GESTATIONAL DIABETES MELLITUS

Acceptance date: 24/09/2024

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Abstract: Introduction: Polycystic ovary syndrome (PCOS) is defined as an endocrinological and metabolic pathology, being this the most common one that affects only in the fertile age of women, manifesting hyperandrogenism, ovulatory alteration and ovaries conformed by several cysts diagnosed through the Ferriman - Gallwey criteria and the Rotterdam criteria. On the other hand, gestational diabetes is diagnosed in pregnancy, characterized by a lack of tolerance to carbohydrates where there is an increase of glucose in the body, with a prevalence of 7% worldwide. It is diagnosed by means of the two ADA strategies that consist in quantifying fasting plasma glucose and by means of the oral glucose tolerance test in one and two hours. Complications can occur in the mother and fetus. **Objective:** To relate PCOS as a risk for developing gestational diabetes mellitus. **Research Question:** Is polycystic ovary syndrome a risk factor for gestational diabetes? **Methods:** Systematic correlational review with a quantitative approach. It was searched in databases such as SCIELO, PUBMED, SCOPUS, SPRINGER, UP TO DATE, GOOGLE ACADEMIC and COCHRANE. **Result:** OR greater than 1 indicating that PCOS is a triggering factor for GDM compared to those without OS thus finding a direct relationship between these two.
Keywords: polycystic ovary, gestational diabetes mellitus, glucose, ovulation.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is defined as a pathology that alters the endocrinological and metabolic system in the female reproductive stage, influenced by environmental and genetic factors; characterized by hyperandrogenism, where multiple cysts are present in the ovaries due to several cysts caused by an ovulatory alteration. (1). It is the most common endocrinological pathology in the female sex exclusively in fertile age, with a worldwide prevalence of approximately 15%, where Latin America represents the highest prevalence with a rate of 5 to 15%. In Ecuador the incidence rate is between 6 to 12%. (2). For its diagnosis it presents a variety of criteria, where initially the symptoms previously described are considered, such as clinical hyperandrogenism conformed by acne, alopecia and hirsutism, (to value with the Ferriman - Gallwey scale with a score > 8). In addition, the Rotterdam criteria are established, consisting of biochemical hyperandrogenism, oligo-anovulation and visualization of the ovaries consisting of several cysts (one of a volume > 10 cm3 or ≥ 12 follicles of a size of 2 to 9 mm in diameter); the existence of two elements allows the diagnosis of PCOS. Increased serum androgen levels are observed in laboratory tests (1).

Several bibliographies determine that there is a relationship between polycystic ovary syndrome, gestational diabetes and type 1 diabetes mellitus, the latter being an impediment for those who seek motherhood, however, those who manage to become pregnant have a high risk of developing comorbidities during pregnancy (3,4). Gestational diabetes (GD) is defined as the pathology presented and diagnosed in pregnancy, characterized by an abnormality in carbohydrate metabolism, providing a lack of tolerance to carbohydrates. (5). In 2019 the worldwide prevalence of GD was 7%, with Latin America occupying the highest rate between 10 to 33% approximately, while its incidence worldwide is 10% per year (6). Likewise, in Ecuador, a figure of 142 to 1084 cases per hundred thousand inhabitants was found, where the highest prevalence is integrated by Ecuadorian women of the coastal region, specifically Manabi, (7). For its diagnosis criteria were established by the American Diabetes Association in 2023, this includes two strategies that are performed between 24 and 28 weeks of gestation in

non-diabetic pregnant women, where the first strategy mentions "cut-off points in fasting of 92 mg/dl, and when performing an oral glucose tolerance test of 75g in one hour of 180 mg/dl and two hours of 153 mg/dl. The diagnosis of GDM is established upon exceeding the above plasma glucose values." (7). On the other hand, "the two-step strategy is initially executed a 50g glucose load test without fasting, where the hourly glucose is measured, if these levels are 130, 135 or 140 mg/dl, the second step is carried out, whereby, the diagnosis of GD is reached if two of the subsequent tests exceed the criteria, which are: fasting 95 mg/dl, and a fasting 100g oral glucose tolerance test in one hour of 180 mg/dl, in two hours of 155 mg/dl and in three hours of 140 mg/dl" (7). In our country, in 2014 the clinical practice guideline of the MSP, known as the Ministry of Public Health (8), establishes that all pregnant women in the initial prenatal consultation should have their risk factors for GD established, classifying them into groups of moderate (BMI > 25, adverse obstetric history) and high risk factors (Latino/Hispanic population, BMI > 30, history of GD, glycosuria, etc.), due to the fact that screening depends on this classification. Those at high risk should have a fasting glucose, if it is "> 126 mg/dl it is interpreted as previous diabetes, between 92 to 126 mg/dl it is considered GD, and < 92 mg/dl the first diagnostic strategy established by the ADA 2023 is performed." (8). Also, in patients at moderate risk, the first strategy mentioned by the ADA 2023 is used, previously described (9).

The ADA (6) mentions that GDM causes complications in 7% of all pregnant women, 50% may develop type 2 DM from 5 to 10 years postpartum and 10% metabolic syndrome. Other complications are: polyhydramnios causing premature rupture of membranes leading to infections, premature delivery, miscarriages, etc. Ketoacidosis can cause coma, increasing the risk of fetal death by 50%. On the other hand, fetal complications are fetal macrosomia leading to dystocia at delivery. Postpartum, neonatal hypoglycemia and childhood obesity of the child may occur.

The aim of this systematic review is to establish polycystic ovary syndrome as a risk factor for gestational diabetes mellitus by meta-analysis of scientific articles from the last 5 years. Which has as specific objectives to determine the magnitude of the relative risk of developing GDM in women with PCOS, to identify additional risk determinants, and to evaluate the variability of GDM frequency among women with PCOS in different populations.

METHODS

This systematic review is a correlational research with a quantitative approach. Its search was in a database such as SCIELO, PUBMED, SCOPUS, SPRINGER, UP TO DATE, GOOGLE ACADEMIC AND COCHRANE, using keywords being as "gestational diabetes", "SOP and risk factors", giving a total of 49 articles belonging to: SCIELO 3; PUBMED 26; SCOPUS 6; SPRINGER 5; UP TO DATE 1; GOOGLE ACADEMIC 4; AND COCHRANE 4, according to this the exclusion criteria were applied: publications older than 5 years of publication, little relevant information and low reliability, and in inclusion criteria were those documents that contribute to the research relevant information, date of the last 5 years of publication (2019-2024), Spanish or English language, reliability and impact of the article, leaving in total 25 articles of which, 12 were used for the meta-analysis and 13 used to collect information about the disease being this diabetes caused by pregnancy and syndrome known as Stein-Leventhal or polycystic ovary.

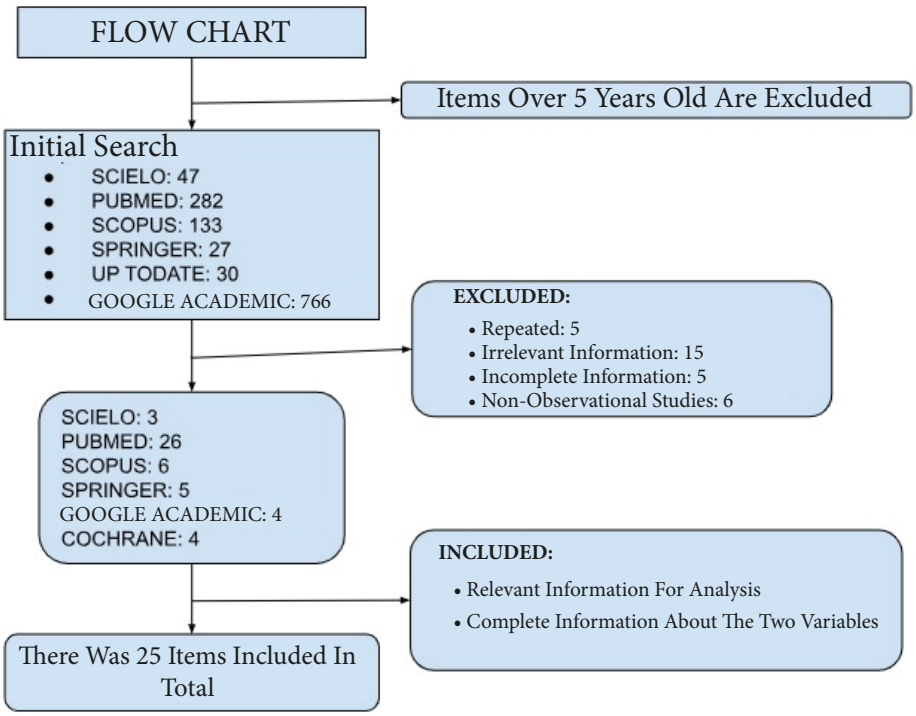

Figure N°1: *Flow chart on item selection.*

RESULTS

An analysis of several studies was conducted to evaluate the relationship between polycystic ovary syndrome (PCOS) and gestational diabetes mellitus (GDM). The results of the 12 studies reviewed consistently indicated that women with PCOS have an increased risk of developing GDM compared to those without the condition.

Barros G. et al. reported that women with risk factors such as obesity, PCOS and hypertension have three times the risk of developing GDM (OR 3.00, CI 1.04-8.45). (9). Ban M, et al. reported a 51% increased odds of GDM in women with PCOS (OR 1.51, CI 1.17-1.94). (10). On the other hand, in population-based studies, women with PCOS had an increased risk of 71% for the development of GDM (11). (111). It was estimated that the latter are between 14.64 and 28.3 times more likely to develop GDM compared to those without PCOS (12). (12).

The information gathered comes from studies analyzing the relationship between PCOS and GDM in different populations and clinical settings. Of these studies, four provide data on how risk factors, including obesity, PCOS, and hypertension can trigger the development of GDM. Another four studies investigated the complications that can arise in pregnant women with PCOS and their impact on the development of GDM. The last four studies explored various aspects of the association between PCOS and GDM in different clinical settings and populations (*Annex N°1*).

In addition, a forest plot is presented with the ORs and confidence indices for each study found. The results reveal that all the ORs present figures greater than 1, which is indicative of high risk in the development of GDM in women with PCOS compared to those without PCOS. Therefore, it is estimated that women with PCOS are approximately 1.5 to 3 times more likely to develop GDM compared to women without PCOS.

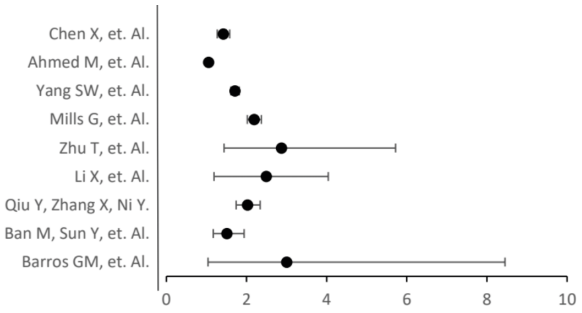

Figure N°2: *Forest plot between SOP relationship for the development of DMG.*

DISCUSSION

The following is an analysis of the studies used in search of the relationship between PCOS and GDM. In a case-control study, Barros G, et al. showed that women with risk factors such as obesity, PCOS and hypertension (OR 3. CI: 1.04 - 8.45) are three times more likely to have GDM. However, due to the breadth of the CI, there is some uncertainty surrounding the exact magnitude of this association (9). In contrast, Ban M, et. al. in a meta-analysis compiling data from 33 studies, demonstrated that women with PCOS are 51% more likely to develop GDM (OR: 1.51. CI 1.17-1.94) compared to those without PCOS, a statistically significant finding (10). Similarly, Qui Y, et. al. found the same association (OR: 2.02. CI: 1.74 - 2.34) in the retrospective and prospective studies they included, in which an analysis of the subgroups that presented PCOS with GDM was carried out, determining that the risk is higher in Caucasian and Asian populations (OR: 2.47. CI: 1.99-3.07). (13).

According to Xiaocui Li, et al. the prevalence of GDM in PCOS patients was 23.98%. In a sample of 196 individuals only 47 had suffered from GDM, the independent risk factors identified for GDM included age ≥ 30 years, elevated BMI (≥24 kg/m²) and higher insulin resistance index. This shows that patients with PCOS are 2.49 times more likely to experience GDM compared to the unexposed group (14). In contrast, Tiantian et al. reported that the prevalence of GDM in PCOS patients was between 5 to 10%, suggesting that PCOS may cause diabetes, but also indicating that there are additional factors beyond BMI that contribute to the risk of GDM (15).

Mills G., et al. mentioned that there is a twofold increased risk of developing GDM in patients with PCOS (OR: 2.19, CI: 2.19-2.37). They also indicated that in patients with PCOS and multiple fetuses, the risk of GDM is statistically significant (OR: 2.33, CI: 1.92-2.83). However, an increased risk of hypertension (HT) in pregnancy was observed in women with PCOS and multiple fetuses (OR: 1.92, CI: 0.99-1.42). (16). Similarly, Yang S., et al. in their cohort study of more than 27,000 women with a history of PCOS confirmed the relationship between PCOS and GDM (OR: 1.71, CI: 1.61-1.82). They also mentioned an increased risk of HT during pregnancy (OR: 1.24, CI: 0.94-1.64), but concluded that the latter relationship is still not entirely clear, recommending further studies on the subject to improve prenatal counseling and treatment for women with PCOS(11).

Ahmed M et al. studied a population of 1,268,901 women, of whom 387,748 had maternal PCOS and 881,153 did not. They showed that obesity can trigger GDM in 4.9% of cases, while PCOS presents an even higher risk, with 6% and an adjusted relative risk (RR: 1.05, CI: 1.03-1.06). The latter indicates that PCOS is associated with a slightly increased risk of developing GDM. Although the increase in risk is relatively small, it is statistically significant according to the confidence interval (17).

Qingzi Y., et al. state that the incidence of GDM among women with PCOS varies greatly among studies, ranging from 4.12% to 59.50% (CI 14.64-28.3), meaning that women with PCOS are between 14.64 and 28.3 times

more likely to develop GDM than women without PCOS (11). (11). Similarly Panagiotis A, et al. report that there is a higher risk of having DM2 compared to those without PCOS (RR: 1.45), being notably higher in women with PCOS who are obese. The results obtained from this research is that patients with a history of PCOS may develop 3.85 times more likely to have GDM compared to women without PCOS (RR: 3.85. CI: 1.99-7.43 and p: <0.001) suggesting a significant association and an accurate estimate of relative risk. This supports the conclusion that PCOS is associated with a higher risk of GDM (18).

A population-based cohort study published with Xinxia Chen, et al. comparing the risks of total and spontaneous preterm delivery between mothers with PCOS and different types of diabetes (non-insulin-treated type 2 and GDM), adjusted for maternal and birth factors, yielded an OR of 1.42, a CI of 1.27-1.58 and a P of 0.0001, showing that there is strong statistical evidence between PCOS patients and those with GDM causing preterm births.0001 showing that there is strong statistical evidence between patients with PCOS and those with GDM leading to preterm births, since, in mothers with GDM, the risks of preterm delivery remain elevated for those with PCOS even after adjustment for maternal and maternal factors (19). This coincides with a study conducted in Massachusetts where in a sample of 91,825 deliveries, 3.9% of the mothers had PCOS and had a 51% higher relative risk of GDM and that newborns born to women with a history of PCOS were more likely to be born preterm (RR 1.17 CI 1.06-1.29) and to be born by prolonged labor (20).

Abbas A, et al. indicated that PCOS will increase the risk of developing GDM, which has resulted in 40% of pregnancies with PCOS becoming complicated (21). This article coincides with the cohort study of Manoharan V, Wong VW., which was conducted between 2015-2019 to 1545 women previously diagnosed with GDM, which were grouped into two groups (with and without PCOS) to determine the impact of PCOS in women with GDM, which concluded that the coexistence of both disorders cause high risk of preeclampsia in pregnant women (22).

In the observational analytical study conducted by Iturrizaga, carried out in 2020, in women between 15 and 49 years of age, divided into two groups, 116 women with diabetes and 232 without diabetes. It was found that those who developed this pathology had a history of PCOS, had twice the risk of suffering from this alteration (OR= (OR=1.655; 95% CI, 1.043 - 2.626), with a significant association (P=0.042). (23). On the other hand, according to Hinostroza M, PCOS is not significantly related to GDM in women 40 years of age or older, because his study presents a p-value = 0.780, which is not statistically significant, OR = 1.325, 95% CI = 0.475 - 3.697.(24).

Galicia S., et al., in their retrospective study conducted in 2020 with pregnant patients between 19 and 30 years of age attended at the Hospital de Salina Cruz, Oaxaca, determined that PCOS is not a significant risk factor for GDM. Instead, they identified that the main risk factor is overweight (25).

CONCLUSION

Finally, with this systematic review based on the analysis of the data that were analyzed, they conclude that women with multiple ovarian cyst syndrome are approximately 1.5 to 3 times more likely to acquire diabetes during pregnancy, as opposed to those who do not have this condition.

In addition, it should be considered that the development of GDM will depend on risk factors such as obesity, persistent high blood pressure and insulin resistance, which play an important role in the development of GDM in women with this condition.

The incidence of GDM in women with PCOS varies significantly among the studies reviewed, with rates ranging from 4.12% to 59.50%. This variability constitutes a need to consider population or contextual variations when assessing diabetes risks in women with the presence of PCOS.

RECOMMENDATIONS

- Perform tests for early detection of diabetes in women in family planning and of childbearing age who have a history or factors that predispose them to risk.
- Perform early glucose testing in pregnant women before 15 weeks who have a history of any factor such as polycystic ovarian disorder for diagnosis of gestational diabetes.
- Control glucose in women with a history of diabetes mellitus during pregnancy, childbirth and postpartum, with PTOG or FPG tests (fasting for at least 8 hours).

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