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Review Article

# Women with Polycystic Ovarian Syndrome. A Clinical Entity with a High risk of Developing Diabetes Mellitus and Gestational Diabetes: Perspectives of an Ideal Treatment

**Juan Carlos Paredes Palma[1*], Carlos Ramirez Velázquez[2], Mario Alberto Huesca Rodriguez[3], Lorena Balladares Macedo[4], Claudia N Paredes Palma[4], Erik Osvaldo Sanchez Hernández[5], Beatriz Irene SanchezTrampe[6], Daniel López Hernandez[7], Georgina González Zárate[8]**

1Head of teaching and research delegation south area of the issste.
2Research coordinator in the delegation south area of the issste.
3Medical delegate of the south area of issste.
4Specialist in gynecology and obstetrics addressed to the churubusco issste clinic of specialties.
5Head of teaching and research of the churubusco issste clinic of specialties issste.
6Coordinator of teaching and research of the "dr. Dario fernandez fierro" hospital of the issste.
7Clinical researcher of the medical subdelegation of the south area of the issste.
8Clinical researcher of the medical subdelegation of the south area of theissste

***Corresponding Author:** Juan Carlos Paredes Palma, Head of teaching and researchdelegationsoutharea of the issste.

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Polycystic Ovarian Syndrome is a syndrome of ovarian dysfunction whose main characteristics are hyperandrogenism, hyperandrogenemia and the presence of polycystic ovaries. This syndrome affects a percentage of between 5 to 10% of women of reproductive age [1]; however, in Mexican-American women a prevalence of 12.8% has been reported. In 2010, Moran et al. They conducted a prospective cross-sectional study in 150 Mexican women to determine the prevalence of PCOS in this population. By Rotterdam criteria, a prevalence of 6.6% was found (95% CI: 2.3-10.9%) [2, 3, 4]. Its etiology remains unknown and is the most common cause of infertility in developed countries [1].

Polycystic Ovarian Syndrome is associated with important metabolic alterations. The prevalence of Diabetes Mellitus 2 is 10 times higher in women with PCOS than among women without this entity. An alteration in glucose tolerance, or the development of Diabetes Mellitus 2 is found in 30 to 50% of women over 30 years of age obese with PCOS, so screening for glucose intolerance has been recommended in women with PCOS [3]. The prevalence of metabolic syndrome is 2 to 3 times higher among women with PCOS than among women without this entity and 20% of women with PCOS under 20 years of age have metabolic syndrome [1]. There is also a significant risk among patients with PCOS of developing Gestational Diabetes [5].

A significant number of patients with PCOS are overweight and many are obese; however, obesity is not considered as a cause for the development of this syndrome [6].

Regarding Pathophysiology in studies, it is suggested that teak cells in women with Polycystic Ovarian Syndrome are more efficient in the conversion of androgenic precursors to testosterone than teak cells in normal women. The concentration of LH has a relative increase over FSH and the ovaries preferentially synthesize androgens. An increase in the frequency of the pulses of the Gonadotropin Releasing Hormone (GnRH) was observed. The increase in the frequency of GnRH pulses favors transcription of the Beta subunit of LH over the Beta subunit of FSH [5].

The role of insulin in the pathophysiology of PCOS is very important because it acts in synergy with LH to increase the synthesis of androgens in the cells of teak and the ovaries of women with PCOS seem to have greater sensitivity to the effect of insulin, perhaps hypersensitivity to it, even when the classic white organs of insulin, such as muscle and fat, show resistance to its action. [6, 7, 8].

Insulin prevents ovulation both by direct affection of follicular development and by the indirect increase of intra-ovarian androgen levels or alteration of gonadotropin secretion. A decrease in circulating insulin levels results in an increase in the frequency of ovulation or menstruation, reduction of testosterone concentrations or both [1].

Metformin is the most widely used biguanide for the treatment of type 2 diabetes mellitus worldwide. Its most important action is the inhibition of hepatic glucose production but also increases the sensitivity of peripheral tissues to insulin. Increased insulin sensitivity, which contributes to the efficacy of metformin in the treatment of diabetes, has also been found in non-diabetic women with polycystic ovarian syndrome [1].

In women with PCOS, long-term treatment with metformin can increase ovulation, improve menstrual cyclicity and reduce androgen levels; the use of metformin can even improve hirsutism. However, it has not shown any risk modification to develop DM2 [1,9].

The results of a randomized clinical study reported in 1998, that pretreatment with metformin, compared with placebo, increased the incidence of ovulation after a subsequent

treatment with clomiphene. The meta-analysis of Lord and cols in 2002 included data from 13 trials and 543 women with PCOS and concluded that metformin is effective and increases the frequency of ovulation (odds ratio, 3.88, 95% confidence interval, 2.25 to 6.69) [9,10].

The signals derived from the intestine and stimulated by the intake of oral nutrients have an important role in the release of insulin. Studies suggest that glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) represent the dominant peptides in most intestinal Insulin-stimulating hormones.

GIP and GLP-1 are members of the glucagon peptide superfamily and share amino acids [11].Incretins increase insulin secretion in a glucose- dependent manner by activation of other specific β-cell receptors [11].An intracerebroventricular injection of GLP-1, or GLP-1 receptor agonists, produces a reduction in food intake that is associated with weight loss in some but not in all studies [11].

There are other actions of GLP-1 on the β cell independent of the acute stimulation of insulin secretion. GLP-1R agonists (GLP-1 receptor) also promote insulin biosynthesis, proliferation of β-cells and stimulate exocrine or precursor cells towards greater differentiation to the β cell phenotype. The increase in the volume of the β cell dependent on GLP-1 receptors has been demonstrated in several experiments in animals. The expansion of the β cell after the administration of GLP-1R receptor agonists prevents or delays the incidence of Diabetes Mellitus in mice [12].

GLP-1 also activates anti-apoptotic pathways, leading to a reduction in β cell death. Studies in mice have shown a reduction in the activation of caspase 3. The antiapoptotic action of GLP-1R agonists is probably directed to the reduction of peroxide-induced apoptosis of Min6 cells [12].

Giovani Paacini et al. They carried out a study whose objective was the characterization of the secretion of GIP and GLP-1 after a load of 75 g of glucose in women with PCOS without glucose intolerance compared with healthy women. The concentrations of GLP1 were the same in the women with PCOS with respect to the control women in the initial phase of the tolerance curve until 60 minutes and were significantly lower in women with PCOS at 180 minutes of the curve [11].

In a study conducted by Pontikis et al. In 20 women with PCOS who underwent a glucose tolerance curve and isoglycemic test after a night of fasting in a two-week interval, they measured levels of insulin, glucose, C-peptide, GIP and GLP-1. Obese women with PCOS were found to have low levels of GIP concentrations in response to the glucose tolerance curve compared to the control group. Age, sensitivity to insulin (QUICKI), SHBG, and basal GIP did not differ between the control group and patients with PCOS. However, baseline GLP-1 was significantly lower in obese women with PCOS compared to both control groups (p 0.023) and in thin women (p <0.02). The group with PCOS showed a decrease in GIP levels after the glucose load compared to the control group [13,14].

A novel drug, exenatide, is an incretin mimetic that simulates the glucorregulatory properties of GLP-1 [12].

Exenatide therapy often results in a loss of weight which can result in a decrease in insulin resistance. The optimal treatment of PCOS should not only improve anovulation but should also reduce comorbidities such as obesity, insulin resistance and DM2, which are linked to this syndrome [11].

Exenatide, which is an analogue of incretin glp-1, apparently has beneficial effects on the β cell mass when given in pharmacological doses to rodents. The effect of DPP4 inhibitors on the mass of the β cell is less clear. In mice in which diabetes was induced and treated with sitagliptin, it was observed that this drug preserved the β cells of apoptosis but there was no increase in the β cell mass [6].

A study conducted by Elkind-Hirsch K. et al. In patients with Polycystic Ovarian Syndrome, overweight and with insulin resistance evaluated the treatment with exenatide and metformin in terms of menstrual cyclicity, hormonal parameters, metabolic profile and inflammatory markers. We included 60 overweight women (BMI> 27) and oligo-ovulation with PCOS, between 18 and 40 years of age [15].

The results of the study showed a statistically significant increase in menstrual frequency in all treatment groups (p 0,001). More regular menses were reported with combination therapy compared with Single-drug therapy (p 0.018). Compared with the baseline, ovulation periods improved in all groups, with a significantly higher proportion with the combined therapy (p 0.01) [15].

The weight decreased significantly from the first to the last visit in all groups (p 0.001).The reduction in body weight was associated with an increase in menstrual frequency significantly (p <.006) [15].

HOMA-IR decreased significantly with all treatments (p 0.043). Similarly, insulin sensitivity, determined by IS OGTT, improved significantly with treatment (p <0.002). The improvement in sensitivity was significantly higher with combination therapy than with treatment with exenatide alone (p <0.02) but not compared with metformin (p <0.085) [16].

The most frequent adverse effects were gastrointestinal to medium to moderate, nausea was the most frequent adverse effect and was greater during combination therapy [15].

Sitagliptin is a molecule that belongs to the family of selective inhibitors of the enzyme dipeptidyl peptidase 4 (DDP-4) that normally degrades the endogenous incretins GIP and GLP-1 [16].In humans, it has been observed that a daily dose of sitagliptin for 10 days resulted in a nearly double increase in GLP-1 after meals.

A study conducted by Kazutaka Aoki et al. It evaluated the effect of miglitol, sitagliptin and its combination on plasma concentrations of glucose, insulin and incretins in non-diabetic men. The results showed that insulin sensitivity among the group taking sitagliptin significantly improved, endogenous GIP and GLp1 concentrations increased and a statistically significant increase in pancreatic insulin secretion was observed [16].

A systematic review and meta-analysis of drugs belonging to DDP-4 showed that there is no risk of gastrointestinal adverse effects but there was an increased risk of urinary tract infections, headache and especially nasopharyngitis[16].

It has been observed that treatment with insulin-sensitizing drugs (metformin and pioglitazone) improves menstrual cyclicity, fertility and the metabolic profile in patients with polycystic ovary [17]. However, they have no effect on the activity of the beta cell and therefore on the progression to

DM2 or Gestational Diabetes [18,19]. Incretins and DPP-4 inhibitors have been shown to improve the activity of the pancreatic β-cell, inhibit apoptosis, in addition to promoting weight loss due to its anorexigenic effect, thus providing an adequate control of weight and an improvement in fertility [17]. In addition, there was a deficit in the secretion and concentrations of GIP and GLP-1 in women with PCOS [13,14]. In a previous pilot study conducted by Paredes Palma JC et al. The statistically significant effect of sitagliptin on ovarian cyclicity was observed, increasing the normalized rate of menstruation by 60% and observing ovulation in terms of comparable progesterone secretion in women who were treated with Metformin [20]. We carried out an extended study with a larger number of patients with PCOS to compare the use of SitagliptinVs Metformin Vs Metformin + Sitagliptin in patients with PCOS with the same results than pilot, this is about to bepublished.

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