

# INDUCTION OF FERTILITY THROUGH THE MANAGEMENT OF INCRETIN MIMETIC DRUGS IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

Giovanna Sacramento Sluzek Faccioli<sup>1</sup>

Clara Quaresma Viera<sup>2</sup>

Isabelly Cristina Haubert Moreira<sup>3</sup>

Anna Carollina Barbosa Gomes<sup>4</sup>

Janaina Andrea Moscatto<sup>5</sup>

Universidade Evangélica de Goiás – UniEVANGÉLICA<sup>12345</sup>

## ABSTRACT

**Introduction:** Polycystic ovary syndrome (PCOS) is a multifactorial condition caused by an endocrine-metabolic-ovarian disorder affecting women of reproductive age. This pathology is directly associated with infertility in these patients, and, therefore, both lifestyle modifications and pharmacological treatments are tools to attempt reversal of this condition. Among these, therapy with incretin mimetics and antidiabetic drugs is relevant. **Materials and Methods:** An integrative literature review was conducted using the PICO strategy: women exposed to hypoglycemic drugs potentially affecting their fertility. The search was performed in PubMed, Scielo, and the BVS indexers – Medline and Lilacs. A total of 45 articles were identified, but only eight met the selected inclusion criteria. **Results:** Studied incretin mimetics, such as liraglutide and exenatide, were promising in weight reduction as monotherapy; however, when combined with other therapies, results were more significant in terms of weight loss, reduction of serum testosterone levels, and decrease in free androgen concentration. These findings indicated an increase of up to 80% in the pregnancy rate among women with PCOS following the proposed treatments. **Conclusion:** The findings indicate a relationship between pharmacotherapy with incretin mimetics in PCOS and an increased trend in pregnancy rates among these patients.

**Keywords:** Fertility; insulin resistance; drug; pharmaco.

## INTRODUCTION

Polycystic ovary syndrome (PCOS) is a prevalent metabolic dysfunction affecting women of reproductive age, with a prevalence ranging from 6% to 16% depending on the studied population. The main clinical features of PCOS are hyperandrogenism and chronic anovulation. The etiopathogenesis of PCOS is multifactorial; however, affected women present clinical signs and symptoms related to insulin resistance, which may occur with varying degrees of overweight and obesity. Laboratory findings often include elevated blood glucose levels and patient complaints of difficulty losing weight (Febrasgo, 2019).

Medications that reduce insulin resistance can alter the pathological course in women with PCOS, as germ cells exposed to high serum glucose are impaired in androgen conversion, directly affecting ovulation induction. Additionally,

hyperglycemia treatment is associated with weight loss and improvement in lipid profiles, factors essential for the ovulatory induction of healthy oocytes (Davidson et al., 2008).

Incretin mimetics, also known as incretinomimetics, are peptides, currently synthetic, that mimic the actions of glucagon-like peptide-1 (GLP-1). Their primary function is to reduce blood glucose levels, but they also have effects on appetite reduction and control of food cravings. Administered in combination with other antidiabetic agents, such as metformin, sulfonylureas, and/or thiazolidinediones (TZDs), these medications can help restore glycemic homeostasis and promote weight loss (Davidson et al., 2008).

This study aimed to evaluate current literature regarding fertility induction through the management of incretin mimetic drugs in patients with PCOS.

## METHODOLOGY

The bibliographic survey used descriptors from DeCS and MeSH: “Fertility; insulin resistance; (drug or pharmaco),” in PubMed, Scielo, and BVS indexers – Medline and Lilacs. Studies were selected based on the PECO strategy: women exposed to hypoglycemic drugs potentially affecting their fertility. Original research articles published in English or Portuguese between 2019 and 2024 were included. Articles with incomplete presentation, paid access, or not meeting the criteria were excluded. Initially, 45 articles were identified, with eight articles finally included in the study.

## RESULTS

**Table 1. Key information on the studied articles**

<b>AUTOR/ANO</b>	<b>Nome do artigo</b>	<b>Resultado</b>
<i>Cena, Chiovato e E Nappi / 2020</i>	<b>Obesity, polycystic ovary syndrome, and infertility: A new avenue for GLP-1 receptor agonists</b>	<b>O uso de liraglutida isolada reduziu o IMC de 172 pacientes após 3 meses, aumentou a taxa de globulina ligadora de hormônios sexuais e reduziu os níveis séricos de testosterona.</b>
<i>Notaro e Neto. / 2021</i>	<b>The use of metformin in women with polycystic ovary syndrome: an updated review</b>	<b>Pacientes tratadas com metformina tiveram aumento na taxa de ovulação e perda ponderal.</b>

<i>Bednarz et al. / 2022</i>	The role of glp-1 receptor agonists in insulin resistance with concomitant obesity treatment in polycystic ovary syndrome.	Foi comprovado que os agonistas de GLP-1 reduzem os efeitos adversos da obesidade no sistema reprodutor feminino através do tratamento, resultando no dobro de gravidezes no período de 1 ano.
<i>Elkind-Hirsch et al. / 2022</i>	Liraglutide 3 mg on weight, body composition, and hormonal and metabolic parameters in women with obesity and polycystic ovary syndrome: a randomized placebo-controlled-phase 3 study	O tratamento com liraglutida 3mg durante um mês foi suficiente para observar o retorno da função ovulatória com duas gravidezes nesse período.
<i>Papaetis e Kyriacou. / 2022</i>	GLP-1 receptor agonists, polycystic ovary syndrome and reproductive dysfunction: Current research and future horizons.	A terapia com metformina e exenatida em ratas com SOP e resistência à insulina tiveram alterações ovarianas positivas nos ciclos foliculares. 83,3% tratadas com exenatida e 67,7% com metformina recuperaram a função normal do ciclo.
<i>Samarasinghe et al. / 2022</i>	Impact of insulin sensitization on metabolic and fertility outcomes in women with polycystic ovary syndrome and overweight or obesity-A systematic review, meta-analysis, and meta-regression.	A terapia combinada com o fármacos de liraglutida, metformina e exenatida demonstraram aumento na frequência menstrual.

The analysis supports the theory that incretin mimetics, alone or combined with other drug classes, significantly improve the reproductive cycle in women presenting insulin resistance, hyperandrogenism, and obesity, characteristic of PCOS. This directly impacts infertility, as the symptomatic triad forms a pathogenic complex capable of interfering with the reproductive cycle, with the ovaries being the most affected structures and the main cause of anovulatory infertility (Bednarz et al., 2022).

First-line treatment of PCOS is based on drugs that reduce excess adipose tissue, a factor highly related to reproduction. In this context, studied incretin mimetics, such as liraglutide and exenatide, were promising in weight reduction as monotherapy. When combined with prior metformin treatment or combination therapy, results were more significant regarding weight loss, reduction of serum testosterone, decrease in free androgen concentration, and improved menstrual regularity.

Furthermore, the described drug therapy positively affected menstrual frequency. A 2020 network meta-analysis of 14 trials involving 619 women concluded that combined therapy of metformin with GLP-1 receptor agonists or metformin with thiazolidinediones was superior to metformin monotherapy in improving hyperandrogenism (Samarasinghe et al., 2022). Insulin resistance was strongly associated with PCOS, especially in patients with high visceral adipose tissue. In PCOS, hypertrophic adipocytes are linked to metabolic disturbances, and hyperandrogenism promotes pathogenic mechanisms contributing to hyperinsulinemia. GLP-1 analogs reduced fasting glucose and serum insulin levels and exhibited anti-inflammatory and antifibrotic activity in the ovaries (Papaetis & Kyriacou, 2022).

## CONCLUSION

The findings indicate a relationship between pharmacotherapy with incretin mimetics in PCOS and an increased trend in pregnancy rates among these patients. GLP-1 receptor agonists, especially when combined with other antidiabetic drug classes such as metformin, act synergistically on the main metabolic and hormonal causes of PCOS, improving the endocrine axis and representing a promising therapy for reproductive health in women.

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