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The Relationship Between Obesity and Polycystic Ovary Syndrome: Pathophysiology, Clinical Consequences, and Management, A Review.

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Abstract

Background. Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder in women of reproductive age and one of the leading causes of infertility. Insulin resistance plays a central role in its pathophysiology and leads to hyperinsulinemia, which is associated with an increased risk obesity in women with PCOS. Obesity in women with PCOS is associated with a more severe clinical phenotype, including increased risk of infertility, reduced response to ovulation induction, greater psychological burden, and impaired quality of life. First line management consists of lifestyle modification to reduce the risks of complications. The relationship between the multisystemic metabolic disorders, obesity and PCOS, is bidirectional and complex, with insulin resistance and hyperinsulinemia acting as key mediators linking the two conditions.

Aim. This review critically examines the relationship between obesity and PCOS, focusing on underlying pathophysiological mechanisms, clinical consequences, and current and emerging management strategies.

Material and methods. PubMed was used for the research of relevant studies with different combination of keywords; obesity and PCOS, management in obese PCOS women, complications in PCOS, therapeutic management in PCOS, therapeutic management in obese PCOS patients, PCOS and infertility, obesity and infertility and PCOS and lifestyle changes.

Results. The available evidence indicates that obesity is a major modifier of PCOS severity, exacerbating insulin resistance, metabolic dysfunction, infertility and psychological burden. Emerging therapies, including GLP-1 receptor agonists, alpha-lipoic acid, myo-inositol, and D-chiro-inositol, show promising effects on metabolic and reproductive outcomes, although current evidence is limited and heterogeneous.

Conclusions. While emerging therapies demonstrate promising short-term benefits, lifestyle modification remains the cornerstone of management.

Key words: Polycystic Ovary Syndrome; PCOS; Obesity; Metabolic effects; Clinical Consequences; Lifestyle changes; Therapeutic Managements

1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age and is one of the leading causes of female infertility (Cena et al., 2020). The etiology of PCOS is multifactorial and involves genetic, epigenetic, dietary, lifestyle, and environmental factors (Gautam et al., 2025). The most widely used diagnostic criteria worldwide are the Rotterdam criteria, which require the presence of at least two of the following: hyperandrogenism, oligo-ovulation or anovulation, and polycystic ovarian morphology (Gautam et al., 2025; Siddiqui et al., 2022).

Hormonal dysregulation, hyperinsulinemia, and immunological factors play crucial roles in the development of PCOS. Hyperandrogenism is exacerbated by hyperinsulinemia through the stimulation of ovarian theca cells. In addition, abnormal gonadotropin secretion, characterized by an elevated luteinizing hormone (LH) to follicle-stimulating hormone (FSH) ratio of

approximately 2:1 to 3:1, is a common biochemical feature. Increased circulating levels of inflammatory markers, including interleukin-6, tumor necrosis factor-alpha, and C-reactive protein, contribute to chronic low-grade inflammation. Consequently, PCOS is recognized as a multisystem metabolic disorder associated with hormonal imbalance, infertility, dyslipidemia, insulin resistance, cardiovascular disease, obesity, and psychological disorders (Gautam et al., 2025; Siddiqui et al., 2022).

Obesity is a chronic metabolic disease associated with numerous conditions, including type 2 diabetes mellitus (T2DM), atherosclerosis, cardiovascular disease, cancer, and reproductive disorders such as anovulation and PCOS (Alenezi et al., 2023). According to the World Health Organization, obesity is defined as a body mass index (BMI) of ≥30 kg/m² (Piché et al., 2020). Obesity is characterized by excess adipose tissue accumulation and dysregulated secretion of adipokines, resulting in chronic inflammation and metabolic dysfunction. Adipokines are hormone-like mediators that impair insulin sensitivity, promote the production of pro-inflammatory cytokines, and reduce satiety. Obese women have elevated circulating leptin concentrations due to increased adipose tissue mass, which contributes to hypothalamic leptin resistance, impaired satiety, and reduced appetite regulation. Elevated serum leptin concentrations have also been associated with lower pregnancy rates following in vitro fertilization (IVF)(Broughton & Moley, 2017). Adipose tissue is now recognized as an active endocrine organ with important metabolic, endocrine, and immunological functions (Alenezi et al., 2023).

Insulin resistance is a hallmark of PCOS, and the resulting hyperinsulinemia contributes to the development of obesity and T2DM. Hyperinsulinemia promotes preferential fat deposition in the abdominal region, leading to central obesity, while excess adiposity further exacerbates both the reproductive and metabolic manifestations of PCOS (Bates & Legro, 2013; Cena et al., 2020; Patel, 2018). Through its effects on androgen production, insulin resistance also contributes to clinical features such as acne, hirsutism, and ovulatory dysfunction (Gautam et al., 2025). Although PCOS can occur in women with normal body weight, obesity is highly prevalent, with most affected women having a BMI of 30 kg/m² or greater (Patel, 2018). Higher BMI has been consistently associated with lower fertility rates and poorer reproductive outcomes (Cena et al., 2020). Clinically, the coexistence of obesity and PCOS is associated with a more severe phenotype

characterized by reduced fertility, diminished response to ovulation induction, increased psychological burden, and poorer quality of life. The relationship between obesity and PCOS is complex and bidirectional, with insulin resistance and hyperinsulinemia serving as key pathophysiological links between the two conditions.

Given the increasing global prevalence of obesity and its significant contribution to the pathophysiology of PCOS and reduced quality of life, there is growing interest in optimizing management strategies that target weight reduction and metabolic dysfunction. Current therapeutic approaches include lifestyle modification, pharmacological treatment, and bariatric surgery, while emerging therapies continue to expand the available treatment options.

Research objective:

To discuss the relationship between obesity and PCOS, focusing on underlying pathophysiological mechanisms, associated clinical consequences, and current and emerging management strategies.

2. RESEARCH MATERIALS AND METHODS

2.1 Methodology

The narrative literature review was conducted in PubMed databases to identify relevant studies showing the relationship between obesity and PCOS which focused on underlying pathophysiological mechanisms, associated clinical consequences, and current and emerging management strategies. A combination of keywords were used to find studies; “obesity and PCOS”, “management in obese PCOS women”, “complications in PCOS”, “therapeutic management in PCOS”, “ therapeutic management in obese PCOS patients”, “PCOS and infertility”, “PCOS and lifestyle changes”, and “obesity and infertility”. Studies from the year 2011 and older were excluded. Studies published not in English and involving animals were excluded. The selection of literature was conducted independently by each author and added into Mendeley. Only original research, randomized control trials, meta-analysis and systematic reviews were taken into consideration.

3. CONSEQUENCES OF OBESITY AND PCOS

3.1 Clinical consequences

The clinical consequences of obesity in women with PCOS includes an almost fourfold higher risk of impaired glucose tolerance and type 2 diabetes mellitus (DMT2), due to higher BMI which exacerbates insulin resistance (Chudzicka-Strugała et al., 2022; Siddiqui et al., 2022). Clinical features of PCOS, particularly central adiposity, results in excessive fat accumulation in the abdomen, hip, and thighs. The abdominal adiposity leads to promoting androgen secretion, hyperadiponectinemia cytokine secretion, oxidative stress, and hyperinsulinemia (Siddiqui et al., 2022).

The altered hormonal environment associated with obesity is also linked to reduced fertility, particularly in women with central obesity. Obese women commonly suffer from perturbations of the hypothalamic-pituitary-ovarian axis and disturbances in the menstrual cycle, making them three times more likely to suffer from oligo-ovulation or anovulation (Marinelli et al., 2022). Obesity leads to a higher level of leptin circulating due to increased adipose tissue mass, which contributes to hypothalamic leptin resistance, impaired satiety, and reduced appetite regulation. Women with higher serum leptin concentrations have lower pregnancy rates following in vitro fertilization (IVF)(Broughton & Moley, 2017).

Even in the absence of ovulatory dysfunction, obese women remain subfertile. According to the cohort study by van der Steeg et al., which included more than 3,000 women with regular menstrual cycles, fertility declined linearly with each unit increase in BMI above 29 kg/m2 (Broughton & Moley, 2017; Van Der Steeg et al., 2008). Furthermore, in a pilot study conducted by Bellver et al., obese women with infertility and PCOS undergoing ovarian stimulation demonstrated dysregulation of one hundred and fifty-one genes compared with normal weight controls. These findings suggest that obesity may contribute to infertility in PCOS through endometrial dysfunction, potentially impairing implantation in addition to its effects on ovarian dysfunction (Bellver et al., 2011).

3.2 Psychological consequences of obesity and PCOS

Women with PCOS should be routinely screened for psychiatric comorbidities and offered appropriate treatment, since they are at an increased risk of anxiety, depression, binge eating disorders and bipolar disorders. Clinical manifestations such as hirsutism, acne, infertility, and obesity may also negatively affect the patient's self-esteem (Kolhe et al., 2022; Patel, 2018; Teede et al., 2023). Studies show that both depression and PCOS are associated with elevated levels of pro-inflammatory markers (Kolhe et al., 2022). Collectively, these factors reduce the patients mental well being and quality of life, which as a result may negatively affect adherence to treatment, particularly given the high levels of dissatisfaction reported with PCOS diagnosis and management (Teede et al., 2023).

4. THERAPEUTIC MANAGEMENT

4.1 Lifestyle management in PCOS

The first line treatment of choice in women with PCOS is lifestyle modification, including dietary intervention and regular physical activities. Weight management, insulin sensitivity, and inflammatory markers are influenced by dietary habits, caloric intake, and food quality. Diets low in refined carbohydrates and rich in dietary fiber improve insulin sensitivity and help regulate blood glucose levels. Since oxidative stress contributes to insulin resistance, hyperandrogenism, and chronic inflammation, antioxidant rich diets may provide additional benefits. Multiple studies reported that higher dietary intake of a-tacopherol, vitamin C, and B-carotene was associated with significantly reduced odds of PCOS (1,19).

A very low-calorie ketogenic diet (VLCKD) has demonstrated promising improvement in BMI, biochemical markers, and ovarian reserve. A study conducted by Cincione et al. found that after 6 weeks of a VLCKD, participants experienced a reduction in insulin resistance and body fat, resulting in decreased peripheral conversion of excess androgens to estrogens within adipose tissue. This was accompanied by normalization of the LH to FSH ratio, indicating improved hormonal balance. Similarly, Magagnini et al. reported that 25 women with obesity and PCOS who followed a VLCKD for 12 weeks experienced significant reductions in body weight, waist

circumference, and insulin resistance. Levels of sex hormone-binding globulin (SHBG) and progesterone also increased, suggesting improvements in ovarian reserve and luteal function (Magagnini et al., 2022). Although these findings are encouraging, the available evidence is limited to short-term studies, therefore, further long-term studies are needed to establish the safety and efficacy of VLCKD in the management of PCOS (Barrea et al., 2023).

Infertility management

Management of infertility in obese women with PCOS begins with weight reduction and metabolic optimization, as obesity worsens reproductive outcomes and reduces the effectiveness of fertility treatment (Patel, 2018). Proper nutrition, regular physical activity, and behavioral intervention are recommended as first-line therapy for all women with PCOS, even when pharmacological treatment is used concurrently(Bates & Legro, 2013; Cena et al., 2020; Marinelli et al., 2022; Patel, 2018). The evidence for fertility benefit from lifestyle change is directionally favorable but not robust. Chudzicka-Strugała et al. concluded that no single dietary pattern can currently be recommended over another. Concluding that while very low energy diets may achieve clinically significant weight loss, evidence regarding improvements in fertility outcomes remains limited (Chudzicka-Strugała et al., 2022). Bariatric surgery may be considered in selected women with severe obesity, but the available evidence is derived primarily from nonrandomized, and its effects on fertility cannot yet be established with certainty (Kolhe et al., 2022).

Pharmacological management

Pharmacological management of polycystic ovary syndrome (PCOS) is guided by the patient's reproductive goals, metabolic profile, and predominant clinical manifestations. According to the 2023 International Evidence-Based Guideline for the Assessment and Management of PCOS, treatment should be individualized and integrated with lifestyle interventions, which remain the foundation of care(Teede et al., 2023). Combined oral contraceptive pills (COCPs) are recommended as first-line pharmacological therapy for reproductive-aged women not seeking pregnancy, owing to their efficacy in regulating menstrual cycles and reducing clinical hyperandrogenism. Metformin is recommended primarily for women with metabolic

abnormalities, particularly those who are overweight or obese, as it improves insulin sensitivity and may contribute to improvements in menstrual cyclicity and metabolic health. The guideline further emphasizes that treatment decisions should account for the high prevalence of obesity, insulin resistance, cardiovascular risk factors, and psychological comorbidities associated with PCOS (Bates & Legro, 2013; Patel, 2018; Teede et al., 2023).

The increasing recognition of obesity as a central contributor to PCOS pathophysiology has expanded interest in therapies targeting weight reduction and metabolic dysfunction. GLP-1 receptor agonists have emerged as promising agents because they promote clinically significant weight loss, improve insulin sensitivity, and may enhance reproductive outcomes in women with obesity and PCOS (Cena et al., 2020). Obesity is strongly associated with reduced fertility, impaired endometrial receptivity, altered implantation-related gene expression, and adverse pregnancy outcomes, providing a mechanistic rationale for pharmacological strategies that reduce adiposity (Bellver et al., 2011; Broughton & Moley, 2017; Marinelli et al., 2022; Van Der Steeg et al., 2008). Recent evidence also supports the use of complementary insulin-sensitizing compounds, particularly myo-inositol, D-chiro-inositol (DCI), and alpha-lipoic acid (ALA). These agents have demonstrated beneficial effects on insulin resistance, menstrual regularity, and metabolic parameters, while combinations of inositol's and ALA may improve ovarian function and reproductive outcomes (Canosa et al., 2020; Cianci et al., 2015; Guarano et al., 2023). However, although available studies suggest therapeutic potential, the evidence base remains heterogeneous, and further large-scale randomized controlled trials are required to establish optimal dosing regimens and long-term efficacy (Alesi et al., 2022; Guarano et al., 2023).

Emerging evidence indicates that chronic low-grade inflammation plays a significant role in PCOS pathogenesis, with inflammatory pathways such as the NLRP3 inflammasome potentially contributing to insulin resistance, obesity-related metabolic dysfunction, and ovarian abnormalities (Alenezi et al., 2023; Siddiqui et al., 2022). Consequently, nutritional supplements and antioxidant therapies have attracted increasing attention as adjunctive treatments. ALA, a potent antioxidant and metabolic regulator, has shown potential benefits in improving glucose metabolism and insulin sensitivity, while dietary antioxidant intake may influence PCOS risk and metabolic status (Guarano et al., 2023; Shoaibinobarian et al., 2022). Nevertheless, current evidence supports these interventions primarily as adjuncts rather than replacements for

established pharmacological therapies. Overall, contemporary management of PCOS increasingly combines conventional treatments such as COCPs and metformin with targeted metabolic therapies and selected nutraceutical approaches to address the multifactorial endocrine, metabolic, and inflammatory mechanisms underlying the disorder (Alesi et al., 2022; Patel, 2018; Teede et al., 2023).

5. EMERGING THERAPIES IN PCOS

5.1 GLP-1

Glucagon-like peptide-1 (GLP-1) receptor agonists stimulate insulin release in a glucose dependent manner. In women with PCOS, they reduce waist circumference, BMI, serum triglycerides concentrations and total testosterone levels, thereby improving the metabolic abnormalities associated with the syndrome (Austregésilo de Athayde De Hollanda Morais et al., 2024).

In a double blind randomized trial, 72 women with PCOS were assigned to receive either liraglutide, a GLP-1 receptor agonist, or placebo. Over 26 weeks, bleeding patterns, anti-Mullerian hormone levels, sex hormones, gonadotropins, and ovarian morphology were evaluated. Women treated with liraglutide were associated with an improvement in bleeding patterns, increased SHBG levels, reduced free testosterone concentrations, and decreased ovarian volume compared with the placebo group (Cena et al., 2020).

Additional studies have evaluated the effect of liraglutide on fertility outcomes. In a prospective randomized open-label study, 28 infertile obese women with PCOS were assigned to receive either metformin alone or metformin combined with low-dose liraglutide. Combination therapy resulted in higher IVF pregnancy rates than metformin alone, despite comparable weight reduction in both treatment groups (Cena et al., 2020; Salamun et al., 2018).

5.2 Alpha lipoic acid

Alpha lipoic acid (ALA) reduces food intake and enhances glucose uptake through suppression of hypothalamic AMP-activated protein kinase (AMPK), which mimics insulin action and improves

insulin sensitivity. ALA also possesses anti-inflammatory properties by inhibiting Nuclear factor kappa B (NF-kB) signaling pathways, leading to reduced production of pro-inflammatory cytokines and therefore potentially alleviating PCOS symptoms. (Alesi et al., 2022; Cianci et al., 2015).

In a retrospective study conducted by Cianci et al., 46 women of reproductive age diagnosed with PCOS according to Rotterdam criteria were included. Twenty-six women received a combination of ALA and D-chiro-inositol (DCI), while 20 served as controls. Women receiving ALA and DCI demonstrated improvements in menstrual regularity, reductions in the number of ovarian cysts, and decreases in BMI and insulin levels compared with the control group (Alesi et al., 2022; Cianci et al., 2015).

A systematic review concluded that ALA has beneficial effects in women with PCOS, particularly when combined with myo-inositol (MYO). This combination improved insulin resistance, especially in overweight or obese women and those with a family history of DMT2. Furthermore, implantation and live birth rates following IVF were higher among overweight or obese women with PCOS treated with ALA and MYO (Canosa et al., 2020; Guarano et al., 2023).

6. DISCUSSION

PCOS is a complex endocrine and metabolic disorder in which obesity substantially worsens both reproductive and metabolic outcomes. Although obesity is not a diagnostic criterion for PCOS, the evidence reviewed in this paper proves that excess adiposity amplifies the severity of the disease through several pathophysiological mechanisms, particularly insulin resistance. A higher BMI is associated with increased insulin resistance, which contributes to a greater risk of impaired glucose tolerance and T2DM (Chudzicka-Strugała et al., 2022; Siddiqui et al., 2022). Central obesity, a common feature in PCOS, is associated with reduced fertility due to alterations in the hormonal environment, disruption of the hypothalamic-pituitary-ovarian axis, and menstrual irregularities leading to oligo-ovulation or anovulation (Marinelli et al., 2022). These findings suggest that obesity exacerbates, rather than causes, the metabolic abnormalities characteristic of PCOS.

Consequently, interventions that improve insulin sensitivity are likely to benefit both metabolic health and reproductive function.

The available evidence also highlights the detrimental effects of obesity on female fertility. Excess adipose tissue alters endocrine function through increased leptin concentrations, peripheral aromatization of androgens, increased production of pro-inflammatory cytokines, and disruption of hypothalamic-pituitary-ovarian axis function. Elevated leptin levels resulting from increased adiposity are associated with lower pregnancy rates following IVF (16). Furthermore, a cohort study demonstrated that obese women remain subfertile even in the absence of ovulatory dysfunction (Broughton & Moley, 2017; Van Der Steeg et al., 2008). Bellver et al. also reported an association between obesity and infertility in women with PCOS that may involve endometrial dysfunction, potentially impairing implantation in addition to ovarian dysfunction (Bellver et al., 2011). However, these findings are based on relatively small cohorts and require confirmation in larger prospective studies. Overall, the evidence suggests that obesity adversely affects fertility through multiple mechanisms involving both ovarian and endometrial dysfunction.

An important observation throughout the literature is that the increased severity of PCOS also contributes to poorer mental well-being and reduced quality of life, which may negatively affect adherence to treatment (Teede et al., 2023). Obesity may further intensify these psychological consequences through social stigma and body image concerns. These findings support that psychological screening should be incorporated into the routine management of women with PCOS.

Lifestyle modification remains the first line treatment for women with PCOS. Dietary intervention and regular physical activity consistently improve weight management, insulin sensitivity, and inflammatory markers (Gautam et al., 2025; Shoaibinobarian et al., 2022). Among dietary strategies, the VLCKD has demonstrated promising short-term improvements in BMI, biochemical markers, and ovarian reserve. However, the available evidence is limited by small study populations and short intervention periods. Therefore, further long-term studies are needed to establish safety, sustainability, and efficacy of VLCKD before it can be recommended over other evidence based dietary approaches(Barrea et al., 2023; Magagnini et al., 2022).

The current international guidelines recommend that pharmacological treatment should be individualized according to each patient's reproductive goals and metabolic profile should complement rather than replace lifestyle interventions (Teede et al., 2023). Metformin is recommended for women with obesity and insulin resistance, whereas COCPs remain the first line pharmacological treatment for women who are not seeking pregnancy because of their efficacy in regulating menstrual cycles and reducing clinical hyperandrogenism (Bates & Legro, 2013; Patel, 2018; Teede et al., 2023). More recently, recognition of obesity as a major contributor to PCOS pathophysiology has led to increasing interest in GLP-1. These agents promote clinically significant weight loss, improve insulin sensitivity, and may enhance reproductive outcomes (Cena et al., 2020).

Similarly, ALA has demonstrated potential therapeutic benefits by reducing oxidative stress and production of pro-inflammatory cytokines, thereby improving metabolic dysfunction associated with PCOS. Several studies show that ALA has proven to be more effective when combined with DCI or MYO. Combination therapy with ALA and DCI has been associated with improved menstrual regularity, reductions in the number of ovarian cysts, and decrease in BMI and insulin levels (Alesi et al., 2022; Cianci et al., 2015). Likewise, the combination of ALA and MYO has demonstrated improvements in insulin resistance, particularly in overweight or obese women with PCOS and those with a family history of DMT2, while also increasing implantation and live birth rates following IVF. Although these findings are encouraging, many studies included small sample sizes, and additional controlled trials are needed to determine the optimal treatment regimens and long-term efficacy of these emerging therapies.

After thoroughly reviewing the current evidence there are several limitations that should be acknowledged. Many of the studies included relatively small sample sizes and short interventions periods, limiting the ability to evaluate long-term outcomes. As well, considerable heterogeneity exists regarding participant characteristics, severity of obesity, and treatment protocols, making direct comparison between studies difficult. Future research should prioritize large randomized controlled trials with extended follow-up to determine the long-term effectiveness and safety of emerging therapeutic therapies.

Overall, the available evidence indicates that obesity is a major modifier of PCOS severity rather than simply a coexisting condition. Obesity independently increases the risk of infertility, and its coexistence with PCOS is associated with a lower likelihood of natural conception compared with women with PCOS who have a normal BMI. Consequently, management should be individualized and tailored to each patient's clinical presentation and reproductive goals. Effective treatment requires a multidisciplinary approach integrating lifestyle modification, pharmacological therapy, fertility focused interventions, and psychological assessment and support. As our understanding of the pathophysiology mechanism linking obesity and PCOS continues to evolve, therapies specifically targeting obesity are likely to play an increasingly important role in improving reproductive outcomes, long-term metabolic health, and quality of life.

7. CONCLUSION

Obesity significantly impacts the clinical manifestations of PCOS by worsening metabolic, reproductive and psychological outcomes. Through its interaction with insulin resistance, hyperandrogenism, and adipose tissue dysfunction, obesity increases the severity of the disease. Management requires a multimodal approach centered on weight reduction through lifestyle modification, pharmacological treatment, and fertility focused therapies, with interventions tailored to each patient's individual needs. Although significant uncertainties remain regarding optimal treatment strategies and their long-term efficacy and safety, emerging therapies such as GLP-1 receptor agonists, ALA, DCI, and MYO show promising therapeutic potential, lifestyle modification remains the cornerstone of PCOS management. Further studies are needed to determine the long-term efficacy and safety of newer therapies.

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Conflicts of Interest

The authors report no conflict of interest.

AI.

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. **AI** were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and

conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

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