

Obesity, Polycystic Ovary Syndrome, and Infertility: A New Avenue for GLP-1 Receptor Agonists

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Context: Obesity is responsible for an increased risk of sub-fecundity and infertility. Obese women show poorer reproductive outcomes regardless of the mode of conception, and higher body mass index (BMI) is associated with poorer fertility prognosis. Polycystic ovary syndrome (PCOS) is one of the leading causes of infertility, and many women with PCOS are also overweight or obese.

Evidence Acquisition: The aim of the present narrative review is to describe the mechanisms responsible for the development of infertility and PCOS in women with obesity/overweight, with a focus on the emerging role of glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RAs) as a therapeutic option for obese women with PCOS.

Evidence synthesis: Weight reduction represents the most significant factor affecting fertility and pregnancy outcomes. Current experimental and clinical evidence suggests the presence of an underlying pathophysiological link between obesity, GLP-1 kinetic alterations, and PCOS pathogenesis. Based on the positive results in patients affected by obesity, with or without diabetes, the administration of GLP-1 RA (mainly liraglutide) alone or in combination with metformin has been investigated in women with obesity and PCOS. Several studies demonstrated significant weight loss and testosterone reduction, with mixed results relative to improvements in insulin resistance parameters and menstrual patterns.

Conclusions: The weight loss effects of GLP-1 RA offer a unique opportunity to expand the treatment options available to PCOS patients. (*J Clin Endocrinol Metab* 105: e2695–e2709, 2020)

Key Words: obesity, infertility, polycystic ovary syndrome, GLP-1 receptor agonists.

Obesity represents a global pandemic, with profound clinical, social, and economic consequences, both in developed countries and in developing nations.

Worldwide, the prevalence of obesity has nearly tripled since 1975, and more than 1.9 billion adults were overweight in 2016, of whom over 650 million were obese

ISSN Print 0021-972X ISSN Online 1945-7197

Printed in USA

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Received 29 January 2020. Accepted 29 May 2020.

First Published Online 22 May 2020.

Corrected and Typeset 17 June 2020.

Abbreviations: BMI, body mass index; CCK, cholecystokinin; DM, diabetes mellitus; GLP-1, glucagon-like peptide-1; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HPO, hypothalamic-pituitary-ovarian; IVF, in vitro fertilization; LBR, live birth rate; LH, luteinizing hormone; OCP, oral contraceptive pills; OSA, obstructive sleep apnea; PCOS, polycystic ovary syndrome; PYY, peptide YY; SHBG, sex hormone-binding globulin.

(1). Obesity is one of the leading causes of premature death and its consequences are not limited to the adult population; indeed, 41 million children under the age of 5 and over 340 million children and adolescents aged 5 to 19 were overweight or obese in 2016 (1). Given these trends, obesity *per se* shortens the life and health expectancy of the current generation of children in comparison with earlier generations (2).

Women of reproductive age are not spared from this dramatic trend; in the United States, 34% of women in this age group are obese (3). Obesity is responsible for an increased risk of subfecundity and infertility, mainly related to impairment in the hypothalamic-pituitary-ovarian (HPO) axis, poor oocyte quality, and altered endometrial receptivity (4, 5). Obese women show poorer reproductive outcomes regardless of the mode of conception, and higher body mass index (BMI) is associated with poorer fertility prognosis (6). Polycystic ovary syndrome (PCOS) is one of the leading causes of infertility, being the most common endocrine disorder in women of reproductive age. Diagnostic criteria include hyperandrogenism, oligo-anovulation, and polycystic ovary morphology (7), but many women with PCOS are also overweight or obese (8). Adiposity has a strong influence in distinct PCOS phenotypes and affects the management of symptoms and fertility outcomes (9).

The aim of the present narrative review is to describe the mechanisms responsible for the development of infertility and PCOS in women with obesity/overweight, with a focus on the emerging role of glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RA) as a therapeutic option for obese women with PCOS.

Obesity and Fertility in Women

Obesity, a key component of metabolic syndrome, exerts a significant impact on female fertility, primarily due to functional alteration of the HPO axis. Obesity is frequently associated with higher circulating levels of insulin, with subsequent increased ovarian androgen production (10). The excess adipose tissue is responsible for the aromatization of these androgens to estrogen, leading to a negative feedback on the HPO axis and affecting gonadotropin production (11). These alterations are responsible for ovulatory dysfunction and menstrual abnormalities.

Hyperinsulinemia plays a fundamental role in the pathogenesis of PCOS, characterized by oligomenorrhea and hyperandrogenism. The concomitant presence of obesity further increases insulin resistance and exacerbates the symptoms of PCOS (12). On the other hand, the increased androgen production in PCOS causes deposition of visceral fat, which in turn accentuates insulin resistance and hyperinsulinemia, further fueling this vicious cycle (13).

Several studies have shown that obesity is associated with increased time-to-pregnancy. An inverse relationship between increasing BMI and fecundability ratios was demonstrated in 2 large cohorts of Danish women planning pregnancies (4, 14). Of note, subfertility in obese women is present even in the absence of ovulatory dysfunction. Reduced fecundity in eumenorrheic obese women was documented in a large US cohort of more than 7000 women (15). In a Dutch cohort of more than 3000 women with normal cycles, the likelihood of spontaneous conception declined linearly with BMI over 29 kg/m². Corrected for possible related factors, women with high BMI had a 4% lower pregnancy rate per BMI unit increase (5).

Several lines of evidence support a negative impact of obesity also on assisted reproduction techniques (ART) outcomes. Indeed, obesity may prolong the duration of ovulation induction, increase the gonadotrophin dose, decrease the number of mature follicles and oocytes retrieved, and increase the cycle cancellation rate (16). Moreover, obesity may have a negative impact on oocyte and embryo quality. Therefore, fertilization, embryo transfer, implantation, and pregnancy rates have been frequently reported to be low correlating to BMI categories (6, 13). In addition, obesity can make oocyte retrieval and embryo transfer procedures more difficult (6). Finally, several studies indicated an increased risk of miscarriage in obese women in ART cycles. A meta-analysis of these studies showed that women with BMI ≥ 25 kg/m² had significantly higher odds of miscarriage, regardless of the conception method (OR 1.67; 95% CI, 1.25-2.25) (17).

The notion that the extremes of maternal BMI may decrease success rates of fertility interventions and increase maternal-fetal morbidity has prompted many providers to establish BMI cutoffs for fertility treatment (18, 19).

Metabolic syndrome and infertility

Obesity is frequently associated with glucose intolerance, insulin resistance, dyslipidemia, and hypertension. The clustering of these risk factors is usually referred to as metabolic syndrome (20). Many of the abnormalities of metabolic syndrome overlap with those of PCOS, and it is hypothesized that both conditions might share the same pathogenesis, namely, hyperinsulinemia and glucose intolerance (20). A link between PCOS and metabolic syndrome has been documented in several studies (21-23), with a prevalence of metabolic syndrome among women with PCOS ranging between 33% and 46%.

In addition to the negative impact of obesity and insulin resistance on female fertility, metabolic disorders

can directly or indirectly affect the fertility of women by influencing either pituitary-hypothalamic function or ovarian function. In particular, both type 1 and type 2 diabetes mellitus (DM) have been associated with undesirable effects on the women's reproductive axis. Individuals with DM and primary and secondary amenorrhea exhibit low levels of estradiol (24), luteinizing hormone (LH), and follicle stimulating hormone (FSH), which have mostly been associated with a lack of residual insulin secretion (25) and poor metabolic control (26). Furthermore, the "glucotoxic" effect of chronic hyperglycemia on the neurons of the hypothalamus can be responsible for reduced LH response to gonadotropin-releasing hormone (GnRH) stimuli (27).

Hyperglycemia also affects ovarian function in women. Elevated blood glucose levels trigger peripheral insulin resistance. In addition, hyperglycemia can also affect ovarian function via the accumulation of advanced glycation products (27, 28). Collectively, nutrients, especially glucose availability, are crucial metabolic regulators of reproductive function (29, 30).

Type 1 DM is associated with fewer pregnancies and live births (31). However, studies assessing fertility treatments in women with diabetes show that achieving optimal metabolic control is the key factor in ensuring successful pregnancy (24). In addition, in vitro fertilization treatments in women with type 1 DM and optimal metabolic control produce similar outcomes compared to those in nondiabetic women (26).

In addition to insulin resistance and hyperglycemia, also dyslipidemia, typical component of metabolic syndrome, has been suggested to have negative effects on fertility and pregnancy (32). A recent meta-analysis documented that infertile women had statistically significant higher BMI, increased total cholesterol, low-density lipoprotein (LDL)-cholesterol, and triglycerides compared to fertile women (33). A subgroup analysis revealed that total cholesterol, high-density lipoprotein (HDL)-cholesterol, fasting glucose, and fasting insulin were increased only in women with PCOS compared with fertile women, while BMI, triglycerides, and LDL-cholesterol were significantly increased in women with any cause of infertility relative to fertile women. However, the causal relationship between dyslipidemia and infertility remains to be proven.

Weight reduction as a treatment target in women with PCOS or infertility

Considering the impact of obesity and metabolic disorders on fertility, it seems reasonable to assume that weight reduction would provide benefit. Existing literature on the effect of weight loss in obese women desiring

conception is mixed. In a study on 67 obese anovulatory infertile women undergoing a 6-month weight loss program, participants lost an average of 10 kg, and ovulatory function was restored in 60 women (90%), of whom 52 (78%) conceived with a miscarriage rate of 18% (34).

In a cohort of 170 women undergoing in vitro fertilization (IVF), short-term weight loss was associated with a higher proportion of retrieved metaphase II oocytes (35). This association was stronger among women with overweight or obesity at baseline. However, short-term weight loss was not correlated with positive β -hCG test, clinical pregnancy, or live birth rates (LBRs) (35). Another retrospective cohort study involved 52 overweight or obese women with infertility who were referred to weight loss counseling. Patients achieving the goal of 10% weight loss had significantly higher conception rates and LBRs (36).

In a trial involving 49 women with obesity who were undergoing fertility treatment, participants were randomized to an intensive 12-week lifestyle intervention or to a control group. Women allocated to the intervention group achieved an average 6.6 kg weight loss and a significantly higher LBR than the control group (44% vs 14%); they also required fewer treatment cycles (2 vs 4) (37).

In a large randomized trial, 290 women were assigned to a 6-month lifestyle-intervention program preceding 18 months of infertility treatment (intervention group) and 287 were assigned to prompt infertility treatment for 24 months (control group) (38). A discontinuation rate of 21.8% was documented in the intervention group. The average weight loss in the intervention group was 4.4 kg, with 43% reaching the target of 5% weight loss. At intention-to-treat analysis, the primary outcome, represented by the vaginal birth of a healthy singleton at term within 24 months after randomization, occurred in 27.1% of the women in the intervention group and 35.2% of those in the control group.

Despite these mixed results, it should be emphasized that weight loss before conception in women with obesity can reduce risks in pregnancy (39).

The effect of weight loss in obese women with PCOS was also evaluated in some studies. In a clinical trial, 149 women with excess weight and PCOS were randomized to 16 weeks of treatment with oral contraceptive pills (OCPs), lifestyle intervention with weight loss medication (sibutramine or orlistat), or to a combination of OCPs and lifestyle intervention (40). After preconception intervention, women underwent standardized ovulation induction with clomiphene citrate and timed intercourse for 4 cycles. A >6% weight loss

was documented in both the lifestyle and the combined cohorts, associated with higher rates of ovulation compared with the OCP cohort. Although the study was not powered to detect a difference in LBR, a trend toward benefit with the use of the lifestyle intervention was documented (40).

In a secondary analysis of 2 randomized trials on infertile women with excess weight and with PCOS, immediate treatment with ovulation induction was compared with delayed treatment after a lifestyle intervention and weight loss (41). The analysis showed improved ovulation and live birth with delayed fertility therapy preceded by lifestyle modification compared with immediate therapy with clomiphene. Although the first-line therapy for PCOS is weight loss focusing on diet and regular exercise, it is well known that obese women with PCOS often fail to diet and disclose poor adherence to dietary behaviors. Thus, weight loss–targeted dietary modifications alone are usually not able to result in sustainable weight loss, with minimal results in metabolic and reproductive outcomes (42).

Gut-Brain Axis Role in PCOS

Gut, brain, and metabolism are highly interrelated in obesity and DM, as well as in PCOS (43).

The central nervous system finely regulates food intake; however, even gastrointestinal hormones and other complex interactions influence eating behavior. Indeed, gut hormones and the gut-brain axis have several roles in the regulation of body fuel metabolism (44). Orexigenic and anorexigenic peptides mainly secreted in the gut produce short-term signals regarding the body energy status, while information on long-term energy stores is given by the serum levels of adipocyte-derived leptin (45).

The occurrence of obesity and insulin resistance in women with PCOS prompted investigation on underlying neuroendocrine interactions (46). In particular, the level of peripheral peptides in women with PCOS was extensively investigated. Serum levels of orexigenic peptides increase before the meals to promote eating activity and decrease after food intake (47). Ghrelin is the typical peripheral orexigenic peptide. Food consumption increases the levels of anorexigenic peptides such as cholecystokinin (CCK), to stop food intake, and GLP-1 and peptide YY (PYY), to regulate inter-meal periods (47).

Gastrointestinal peptides and adiposity signals regulate appetite through local and central effects (47).

Whether women with PCOS suffer from an alteration in appetite and satiety remains to be established,

as does the role of gastrointestinal hormones in weight management.

In individuals with obesity, serum levels of ghrelin are lower than in lean individuals, and an increase in ghrelin levels is observed after weight loss (48–50). An increase in leptin and insulin levels has been blamed to explain the decrease in ghrelin levels in individuals with obesity; it has also been suggested that this alteration could represent a physiological adaptation of the body to obesity once a positive energy balance is reached (48, 49). Of note, ghrelin suppression, usually seen in lean individuals after meal consumption, is not found in individuals with obesity (48). The inability of food intake to suppress ghrelin levels can contribute to the pathogenesis of obesity.

Different results are available in the literature regarding ghrelin levels in women with PCOS. A meta-analysis of several studies suggests that fasting ghrelin levels are lower in PCOS; however, a significant heterogeneity across the included studies is documented (51). Available data also suggest either blunted suppression or no change of stimulated ghrelin levels in PCOS compared with BMI-matched healthy women. Ghrelin levels were found to be inversely correlated with parameters of hyperandrogenism, insulin levels, and insulin resistance (43).

Among gastrointestinal peptides, great attention has been devoted to GLP-1, a member of incretin hormones along with gastric inhibitory peptide (GIP) (52). Incretin hormones are secreted in the gut following food intake and they exert insulinotropic effects (52). GLP-1 is synthesized by L-cells in the distal small intestine and is secreted in response to food intake. The anorexigenic effects of GLP-1 are mediated by the vagus nerve, which provides communication between the gastrointestinal and the central nervous system (53, 54). Following gastric distension, the stimulation of mechanoreceptors generates satiety signals, which are conducted to brain via vagal nerves (55). GLP-1 slows down gastric emptying and intestinal motility both in healthy lean individuals and in subjects with obesity or type 2 DM (55).

The vagal afferents are, however, not the only entry of GLP-1 signaling to the central nervous system, as all blood–brain barrier-free areas of the central nervous system show high densities of GLP-1 receptors (56). Thus, activation of central pathways involved in appetite regulation by peripheral GLP-1 may occur via the vagus nerve, as well as directly via the area postrema and the median eminence (57). Evidence for a relationship between obesity and GLP-1 levels is mixed, with some studies showing decreased levels of GLP-1 (58–61) and others showing either increased basal GLP-1 or no

significant change (62). Some studies also showed that meal-stimulated GLP-1 levels were lower in individuals with obesity when compared to lean subjects (63–65).

Secretion of GLP-1 after oral glucose tolerance test (OGTT) was evaluated in a group of lean, glucose-tolerant PCOS women in comparison with age- and BMI-matched healthy women (66). The study documented that active GLP-1 levels had a significantly different time-dependent pattern in PCOS ($P < 0.002$ for PCOS versus time interaction). GLP-1 concentrations were similar in PCOS and controls in the early phase of OGTT and then reached significantly lower levels in PCOS than in controls at 180 minutes ($P < 0.05$). These findings suggest that low late-phase active GLP-1 concentrations during OGTT could be used as an early marker of a prediabetic state in PCOS women.

The high prevalence of type 2 DM in PCOS gave birth to the hypothesis that GLP-1 secretion might be altered in this condition. However, women with obesity and PCOS apparently do not differ from controls with obesity in terms of basal and stimulated GLP-1 levels, although results are somewhat heterogeneous and inconclusive (43).

As for the role of other gastrointestinal peptides in women with PCOS, results are mixed about GIP secretion, while basal and meal-stimulated levels of CCK have been found to be similar in women with PCOS as compared with BMI-matched controls (67, 68). Similar basal and postprandial PYY levels in women with PCOS compared with BMI-matched healthy women have also been frequently reported (67–70).

Endocrine and metabolic effects of GLP-1 RAs

Reduction in body weight has been demonstrated to improve hyperandrogenism, reproductive function, and metabolic parameters such as hyperlipidemia, and glycemic control, as well as hypertension, in women with PCOS (71–73). The availability of GLP-1 RAs offers a unique opportunity to simultaneously address both excess body weight and hyperglycemia. GLP-1 RAs are a class of glucose-lowering medications with incretin mimetic activity, approved for the treatment of type 2 DM. A full description of the mechanisms of action of GLP-1 RAs is out of the scope of this review and can be found elsewhere (74). In subjects with DM, the use of GLP-1 RA is associated with a significant reduction of glycated hemoglobin, with weight loss, a modest decrease in blood pressure, and an improvement of hyperlipidemia (75, 76). Recent cardiovascular outcomes trials have shown that some GLP-1 RAs, such as liraglutide and semaglutide, reduce the rate of major cardiovascular events in individuals with type 2 DM (77, 78).

Subcutaneous liraglutide 3 mg once daily is indicated as an adjunct to a reduced-energy diet and increased physical activity for chronic body weight management in adults with a BMI ≥ 30 kg/m² or BMI of ≥ 27 kg/m² and at least one weight-related comorbidity including hypertension, dyslipidemia, type 2 DM, or obstructive sleep apnea.

The efficacy of once-daily subcutaneous liraglutide injection for chronic weight management in adults was established in 5 large-scale randomized multicenter phase 3 trials (Table 1) (79–84). Four of these trials were part of the Satiety and Clinical Adiposity—Liraglutide Evidence in nondiabetic and diabetic individuals (SCALE) program.

In a double-blind, placebo-controlled, 20-week trial, with open-label orlistat comparator, 564 individuals were randomly assigned to 1 of 4 liraglutide doses (1.2 mg, 1.8 mg, 2.4 mg, or 3.0 mg) or to placebo administered once a day subcutaneously, or orlistat (120 mg) 3 times a day orally (79). Mean weight loss with liraglutide 1.2 to 3.0 mg was 4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg compared with 2.8 kg with placebo and 4.1 kg with orlistat. More individuals (76%) lost more than 5% weight with liraglutide 3.0 mg than with placebo (30%) or orlistat (44%). Liraglutide reduced blood pressure at all doses, and reduced the prevalence of prediabetes (84%–96% reduction) with 1.8 to 3.0 mg per day (79). The benefits of liraglutide on body weight and cardiovascular risk factors were maintained over 2 years (80).

In a phase 3 randomized trial, participants with overweight/obesity who lost $\geq 5\%$ of initial weight during a low-calorie diet run-in were randomly assigned to liraglutide 3.0 mg per day or placebo for 56 weeks (81). Participants lost a mean 6.0% of their weight during run-in. From randomization to week 56, weight decreased an additional mean 6.2% with liraglutide and 0.2% with placebo. More participants receiving liraglutide (81.4%) maintained the $\geq 5\%$ run-in weight loss, compared with those receiving placebo (48.9%), and 50.5% vs 21.8% of participants lost $\geq 5\%$ of randomization weight.

A large 56-week, double-blind trial involved 3731 patients without type 2 DM and with BMI ≥ 30 or ≥ 27 if they had treated or untreated dyslipidemia or hypertension (82). Patients were randomly assigned in a 2:1 ratio to receive once-daily subcutaneous injections of 3.0 mg liraglutide or placebo. At week 56, patients in the liraglutide group had lost a mean of 8.4 ± 7.3 kg of body weight, and those in the placebo group had lost a mean of 2.8 ± 6.5 kg. A total of 63.2% of the patients in the liraglutide group, as compared with 27.1% in the placebo group, lost at least 5% of their body weight,

Table 1. Characteristics of the RCTs Exploring the Role of Subcutaneous Liraglutide Injection for Chronic Weight Management in Adults

Study	Participant characteristics	Number randomized	Study duration	Results for liraglutide 3.0 mg vs placebo	Side effects for liraglutide 3.0 mg vs placebo	Attrition rate
Astrup A et al (79)	76% women stable body weight, BMI ≥ 30 kg/m ² and ≤ 40 kg/m ²	Liraglutide 1.2 mg (N = 95) Liraglutide 1.8 mg (N = 90) Liraglutide 2.4 mg (N = 93) Liraglutide 3.0 mg (N = 93) Orlistat (N = 95) Placebo (N = 98)	20 weeks	Body weight: -4.4 kg (95% CI, -6.0 to -2.9 kg, $P < 0.0001$); $\geq 5\%$ body weight loss: 76.1% vs placebo 29.6% ($P < 0.0001$); $\geq 10\%$ body weight loss: 28.3% vs placebo 2.0%	Nausea (47.3% vs 5.1%) Diarrhea (12.9% vs 7.1%) Vomiting (11.8% vs 2.0%) Fatigue (10.8% vs 2.0%) Gastroenteritis (7.5% vs 3.1%)	16.3%
Astrup A et al (80) 2-year extension of (79)	76% women stable body weight, BMI ≥ 30 kg/m ² and ≤ 40 kg/m ²	Liraglutide 1.2 mg (N = 95) Liraglutide 1.8 mg (N = 90) Liraglutide 2.4 mg (N = 93) Liraglutide 3.0 mg (N = 93) Orlistat (N = 95) Placebo (N = 98)	2 years	Body weight: -5.8 kg (95% CI, -8.0 to -3.7 kg, $P \leq 0.001$); $\geq 5\%$ body weight loss: 73% vs placebo 28% ($P \leq 0.001$); $\geq 10\%$ body weight loss: 37% vs placebo 10% ($P \leq 0.001$).	Nausea (48.4% vs 7.1%) Gastroenteritis (23.7% vs 13.3%) Influenza (23.7% vs 10.2%) Constipation (18.3% vs 12.2%) Diarrhea (15.1% vs 10.2%) URI (14.0% vs 9.2%) Fatigue (14.0% vs 8.2%) Vomiting (12.9% vs 2.0%)	23.8%
Wadden et al (81) SCALE Maintenance	81% women, stable body weight, BMI ≥ 30 kg/m ² or ≥ 27 kg/m ² with dyslipidemia or hypertension, loss $\geq 5\%$ of the initial body weight in low caloric diet run-in period (4–12 weeks)	Liraglutide 3.0 mg (N = 212) Placebo (N = 210) Orlistat (N = 95) Placebo (N = 98)	56 weeks	Body weight: -5.9 kg (95% CI, -7.3 to -4.4 kg, $P < 0.0001$); Body weight: -6.1 % (95% CI, -7.5 to -4.6%, $P < 0.0001$); $\geq 5\%$ body weight loss: 50.5% vs placebo 21.8% ($P < 0.0001$); $\geq 10\%$ body weight loss: 26.1% vs placebo 6.3% ($P < 0.0001$); maintenance of $\geq 5\%$ run-in weight loss: 81.4% vs placebo 48.9% ($P < 0.0001$).	Nausea (47.6% vs 17.1%) Constipation (26.9% vs 12.4%) Diarrhea (17.9% vs 12.4%) Vomiting (16.5% vs 2.4%) Decreased appetite (9.9% vs 1.4%) Dyspepsia (9.4% vs 1.9%) Fatigue (8.0% vs 5.2%) Abdominal pain (6.6% vs 1.4%) Hypoglycemia (5.2% vs 2.4%)	27.7%
Pi-Sunyer et al (82) SCALE Obesity and prediabetes	78% women, stable body weight, BMI ≥ 30 kg/m ² or ≥ 27 kg/m ² with dyslipidemia or hypertension	Liraglutide 3.0 mg (N = 2487) Placebo (N = 1244)	56 weeks	Body weight: -5.6 kg (95% CI, -6.0 to -5.1 kg, $P < 0.0001$); Body weight: -5.4% (95% CI, -5.8 to -5.0%, $P < 0.001$); $\geq 5\%$ body weight loss: 63.2% vs placebo 27.1% ($P < 0.001$); $\geq 10\%$ body weight loss: 33.1% vs placebo 10.6% ($P < 0.001$).	Nausea (40.2% vs 14.7%) Diarrhea (20.9% vs 9.3%) Constipation (20.0% vs 8.7%) Vomiting (16.3% vs 4.1%) Decreased appetite (10.8% vs 3.1%) Dyspepsia (9.5% vs 3.1%)	30.6%

Table 1. Continued

Study	Participant characteristics	Number randomized	Study duration	Results for liraglutide 3.0 mg vs placebo	Side effects for liraglutide 3.0 mg vs placebo	Attrition rate
Davies et al (83) SCALE Diabetes	50% women, stable body weight, BMI ≥ 27 kg/m ² , type 2 diabetes (HbA1c 7.0%-10.0%) treated with diet and exercise alone or in combination with 1-3 oral glucose-lowering agents	Liraglutide 3.0 mg (N = 423) Liraglutide 1.8 mg (N = 211) Placebo (N = 212)	56 weeks	Body weight: -4.2 kg; Body weight: -4.0 % (95% CI, -5.1 to -2.9%, <i>P</i> <0.001); $\geq 5\%$ body weight loss: 54.3% vs placebo 21.4% (<i>P</i> <0.001); $\geq 10\%$ body weight loss: 25.2% vs placebo 6.7% (<i>P</i> <0.001).	Hypoglycemia ^a (44.5% vs 27.4%) Nausea (32.7% vs 13.7%) Diarrhea (25.6% vs 12.7%) Constipation (16.1% vs 6.1%) Vomiting (15.6% vs 5.7%) Dyspepsia (11.1% vs 2.4%) Abdominal distension (6.2% vs 1.4%) Abdominal pain (6.2% vs 4.2%) Nausea (26.7% vs 6.7%) Diarrhea (16.5% vs 7.8%) Constipation (11.9% vs 3.4%) Dyspepsia (8.5% vs 0.1.1%) Vomiting (7.4% vs 2.8%) GERD (5.7% vs 0.6%)	25.8%
Blackman et al (84) SCALE Sleep Apnea	28% women, stable body weight, BMI ≥ 30 kg/m ² , moderate to severe OSA, unwilling or unable to use CPAP	Liraglutide 3.0 mg (N = 180) Placebo (N = 179)	32 weeks	Body weight: -4.9 kg (95% CI, -6.2 to -3.7 kg, <i>P</i> <0.0001); Body weight: -4.2 % (95% CI, -5.2 to -3.1%, <i>P</i> <0.0001); $\geq 5\%$ body weight loss: 46.4% vs placebo 18.1% (<i>P</i> <0.0001); $\geq 10\%$ body weight loss: 22.4% vs placebo 1.5% (<i>P</i> <0.0001).		23.1%

^aAmerican Diabetes Association definition.

Abbreviations: BMI, body mass index; CPAP, continuous positive airway pressure; GERD, gastroesophageal reflux disease OSA, obstructive sleep apnea; RCT, randomized controlled trial; URI, upper respiratory tract infection.

moreover 33.1% and 10.6%, respectively, lost more than 10% of their body weight.

In a 56 week double-blind, placebo-controlled trial, 846 patients with overweight or obesity and type 2 DM were randomized in a 2:1:1 ratio to liraglutide 3 mg, liraglutide 1.8 mg, or placebo, all as adjunct to 500 kcal/day intake less than required for weight maintenance and increased physical activity (≥ 150 min/wk) (83). Weight loss was 6.0% (6.4 kg) with liraglutide (3.0 mg dose), 4.7% (5.0 kg) with liraglutide (1.8 mg dose), and 2.0% (2.2 kg) with placebo. Weight loss of $\geq 5\%$ occurred in 54.3% with liraglutide 3.0 mg and 40.4% with liraglutide 1.8 mg versus 21.4% with placebo. Weight loss $>10\%$ occurred in 25.2% with liraglutide 3.0 mg and 15.9% with liraglutide 1.8 mg versus 6.7% with placebo.

Finally, a 32-week, double-blind, randomized trial investigated whether liraglutide 3.0 mg reduced obstructive sleep apnea (OSA) severity compared with placebo in individuals with obesity and without diabetes (84). The study documented a significant reduction in OSA severity, as measured with the apnea-hypopnea index (AHI), in the liraglutide group versus placebo. Liraglutide produced greater mean percentage weight loss compared with placebo (-5.7% vs -1.6%). A statistically significant association between the degree of weight loss and improvement in OSA endpoints was also documented.

A recent meta-analysis of these trials showed that treatment with liraglutide produced an average decrease in body weight of 5.25 kg (95% CI, -6.17 to -4.32), compared with placebo (85).

Recently, the use of GLP-1 RAs has been extended to other conditions such as PCOS.

Liraglutide in PCOS

Effects of GLP1-RA on metabolic endpoints

Several studies have shown that short-term treatment with GLP-1 RAs, either as monotherapy or in combination with metformin, produces significant weight loss and favorable metabolic changes in women with overweight or obesity and PCOS. Clinical studies of GLP-1 RAs in obese/overweight PCOS women are summarized in Table 2. Most of the evidence refers to the use of liraglutide in patients previously treated with metformin. In addition to a relevant effect on weight, some studies documented additional beneficial effects on androgen levels and metabolic parameters (86, 87).

In a 6-month controlled trial, the efficacy of daily liraglutide 1.8 mg on weight loss and markers of atherothrombosis was assessed in 19 women with

obesity and PCOS and 17 controls of similar age and weight. In both groups, liraglutide treatment was associated with weight loss of 3% to 4% and significant reduction in atherothrombosis markers, including inflammation, endothelial function, and platelet function (88).

In a 12-week randomized study, 45 women with obesity and PCOS were allocated to metformin 1000 mg twice daily or liraglutide 1.2 mg daily or roflumilast 500 μ g daily (89). Significantly greater BMI reductions were documented with liraglutide or roflumilast (1.1 ± 1.26 and 0.8 ± 0.99 kg/m², respectively) as compared with metformin (0.1 ± 0.67 kg/m²). The use of liraglutide was also associated with improvements in body composition, as assessed by dual energy x-ray absorptiometry (DXA), including a significant decrease of visceral adipose tissue area.

The effect of liraglutide on ectopic fat was further evaluated in a double-blind, placebo-controlled, randomized clinical trial involving 72 women with PCOS (90). Compared with placebo, 26 weeks of treatment with liraglutide significantly reduced body weight by 5.2 kg, liver fat content by 44%, visceral adipose depot by 18%, and the prevalence of nonalcoholic fatty liver disease by two-thirds.

The results of 7 randomized trials assessing the efficacy of liraglutide in women with PCOS (86–89, 91, 92) have been combined in a meta-analysis (93). The outcomes assessed included BMI and waist circumference, fasting serum insulin levels and insulin resistance as assessed by HOMA-IR, and androgenic status including serum total testosterone and sex hormone-binding globulin (SHBG) concentrations. Liraglutide treatment decreased BMI by 1.65 (0.72–2.58) kg/m² in 172 patients after 3 months. In addition, a decrease in serum testosterone levels was observed, while insulin levels and insulin sensitivity were not reduced, but had high heterogeneity among studies.

Short-term interventions with metformin plus liraglutide 1.2 mg (COMBO) or liraglutide 3.0 mg (LIRA 3 mg) alone led to significant weight loss (-3.6 ± 2.5 kg, $P = 0.002$ in COMBO vs -6.3 ± 3.7 kg, $P = 0.001$ in LIRA3) in obese women with PCOS; liraglutide 3.0 mg was superior to liraglutide 1.2 mg plus metformin in BMI and waist circumference (WC) reduction (BMI: LIRA 3 -2.2 ± 1.3 vs COMBO -1.3 ± 0.9 kg/m², $P = 0.05$; WC: LIRA3 -4.2 ± 3.4 vs COMBO -2.2 ± 6.2 cm, $P = 0.014$) (94).

More recently, a meta-analysis of 8 randomized trials compared the efficacy of GLP-1 RAs versus metformin in women with PCOS (95). A GLP-1 RA was superior to metformin in improving insulin sensitivity

Table 2. Clinical Studies of GLP-1 RAs in Obese/Overweight Women With PCOS

Study	Participant characteristics	Study arms	Study duration	Primary outcome	Other outcomes	Body weight Loss (kg)	Metabolic changes	Menstrual pattern/other	Attrition rate
Elkind-Hirsch et al (86)	Overweight (BMI >27), insulin-resistant, oligoovulatory women. Age 18-40 years. PCOS diagnosed according to a modification of Rotterdam criteria 2003	1) MET:1000 mg bid (n = 14) 2) EXE (10 µg bid) (n = 14) 3) MET 1000 mg bid + EX 10 µg bid (n = 14)	24 weeks	Menstrual frequency	Ovulation rate Insulin action FAI Inflammatory markers	1) -1.6 ± 0.2 2) -3.2 ± 0.1 3) -6.0 ± 0.5	FAI reduced and Insulin sensitivity improved in combination arm	Combination therapy superior to EX or MET (menses and ovulation)	30%
Rasmussen et al (87)	Overweight or obese women, pre-treated with MET for at least 6 months. PCOS diagnosed according to Rotterdam criteria	Add-on of LIRA 1.2-1.8 mg (n = 84)	Mean of 27.8 weeks	Weight loss	-	-9.0 (95% CI, 7.8-10.1)	Mean decrease in BMI of 3.2 kg/m ² Weight loss >5% and >10% in 81.7% and 32.9% of patients, respectively		20.0%
Kahal et al (88)	Obese women (BMI 30-45) Age 18-45 years Healthy controls. PCOS diagnosed according to Rotterdam criteria	LIRA: 1.8 mg (19 obese women with PCOS and 17 controls)	6 months	CV risk markers	Weight loss	PCOS: -3.0 ± 4.2 Controls: -3.8 ± 3.0	HOMA-IR, hsCRP, endothelial adhesion markers significantly and equally reduced in both groups No changes in cIMT		30.6%
Jensterle et al (89)	Obese (BMI ≥30) women Age ≥18 years, premenopause. PCOS diagnosed by ASRM-ESHRE Rotterdam criteria	1) MET:1000 mg bid (n = 14) 2) LIRA 1.2 mg (n = 14) 3) ROF 500 mg qd (n = 14)	12 weeks	Weight loss	Hormonal and metabolic changes	1) -0.8 ± 1.0 2) -3.1 ± 3.5 3) -2.1 ± 2.0	FAI reduction in ROF arm; decrease in visceral fat in LIRA arm. HOMA-IR decreased in all treatment arms. LIRA superior to MET in reducing glucose at 120 min of OGTT	Menstrual frequency increased with all treatments.	8.9%
Frøssing et al (90)	Women with BMI >25 and/or insulin resistance PCOS diagnosed according to Rotterdam criteria	1) LIRA 1.8 mg OD s.c. (n = 48) 2) Placebo (n = 24)	26 weeks	Liver fat VAT Prevalence of NAFLD	Weight change OGTT, SHBG, testosterone	1) -5.2 ± 0.7 2) +0.2 ± 0.9	LIRA reduced liver fat content by 44%, VAT by 18%, and the prevalence of NAFLD by two-thirds. With LIRA, SHBG levels increased by 19%, and free testosterone decreased by 19%.		28%

Table 2. Continued

Study	Participant characteristics	Study arms	Study duration	Primary outcome	Other outcomes	Body weight loss (kg)	Metabolic changes	Menstrual pattern/other	Attrition rate
Jensterle et al (91)	Obese (BMI ≥30), nondiabetic women who had lost ≥5% body weight during pretreatment with MET for at least 6 months. Age ≥18 years, PCOS diagnosed by the NICHD criteria.	1) MET: 1000 mg BID (n = 14) 2) LIRA: 1.2 mg OD s.c. (n = 11) 3) MET 1000 mg BID + LIRA 1.2 mg QD s.c. (n = 11)	12 weeks	Weight loss	Body composition IR	1) -1.2 ± 1.4 2) -3.8 ± 3.7 3) -6.5 ± 2.8	No major changes in fasting glucose, insulin, and insulin during OGTT. Glucose value after 120 min during OGTT significantly reduced in the combination arm vs MET.	No significant changes in menstrual pattern.	10%
Jensterle et al (92)	Obese (BMI ≥30) women with newly diagnosed PCOS. Age ≥18 years, premenopausal, PCOS diagnosed by the NICHD criteria.	1) MET: 1000 mg bid/ daily (n = 14) 2) LIRA 1.2 mg (n = 14)	12 weeks	Weight loss	Body composition IR	1) -2.3 2) -3.0 LIRA superior in severe IR (BMI reduction 2.13 vs 0.62 kg/m ²)	Decrease in total testosterone in MET Increase in LH in LIRA		12.5%
Jensterle et al (94)	Obese (BMI ≥30) women Age ≥18 years, premenopausal, PCOS diagnosed by ASRM-ESHRE Rotterdam criteria	1) MET 1000 mg BID + LIRA 1.3 mg OD s.c. (n = 15) 2) LIRA 3 mg OD s.c. (n = 15)	12 weeks	Weight loss	Metabolic and hormonal changes	1) -3.6 ± 2.5 2) -6.3 ± 3.7	Both interventions resulted in a significant decrease of post-OGTT glucose levels. Combination therapy significantly reduced total testosterone		6.7%
Nylander et al (96)	Overweight (BMI ≥25) women and/or insulin resistance Age ≥18 years, PCOS diagnosed according to Rotterdam criteria	1) LIRA 1.8 mg (n = 44) 2) Placebo (n = 21)	26 weeks	Bleeding pattern	Levels of AMH, sex hormones, and gonadotrophins, ovarian morphology	LIRA vs Placebo: -5.2 (95% CI, 3.0-7.5)	In the LIRA group, SHBG increased and free testosterone decreased. Ovarian volume decreased with LIRA vs placebo.	Bleeding ratio significantly improved with LIRA vs placebo	9.7%
Salamun et al (97)	Infertile, obese women (BMI ≥30) Age ≤38 years, first or second IVF attempt PCOS diagnosed according to revised Rotterdam criteria	1) MET 1000 mg bid (n = 14) 2) MET 1000 mg bid + LIRA 1.3 mg QD s.c. (n = 14)	12 weeks	IVF pregnancy rate	Weight change	1) -7.0 ± 6.0 2) -7.5 ± 3.9		Pregnancy rate per embryo transfer significantly higher with combined therapy (85.7%) compared with MET (28.6%)	18%

Table 2. Continued

Study	Participant characteristics	Study arms	Study duration	Primary outcome	Other outcomes	Body weight Loss (kg)	Metabolic changes	Menstrual pattern/other	Attrition rate
Liu et al (98).	Overweight or obese women (BMI ≥ 24) Age 18–40 years PCOS diagnosed according to Rotterdam criteria	1) MET:1000 mg bid (n = 88) 2) EXE: 10 μ g BID (n = 88)	12 weeks; after 12 weeks all patients treated with MET alone for additional 12 weeks	Weight loss	Fat mass, hormonal levels, insulin resistance, lipid profile, inflammatory marker, menstrual frequency, and rate of pregnancy.	1) -2.28 ± 0.55 2) -4.29 ± 1.29	Decrease in android fat mass% and total fat mass% with EXE, but not with MET. Greater decrease in HOMA-IR and insulin levels with EXE than with MET. HsCRP levels decreased significantly in the EXE group only.	Menstrual frequency increased significantly in both groups. Rate of natural pregnancy significantly higher following EXE treatment than following MET treatment	10.2%

AMH, anti-Müllerian hormone; cIMT, carotid-intima media thickness; EXE, exenatide; FAI, free androgen index; HOMA-IR, homeostasis model assessment-IR; hsCRP, high-sensitivity C-reactive protein; IR, insulin resistance; IVF, in vitro fertilization; LIRA, liraglutide; MET, metformin; NAFLD, nonalcoholic fatty liver disease; NICHD, National Institute of Child Health and Human Development; OGTT, oral glucose tolerance test; PINP, Procollagen Type III N-Terminal Peptide; SHBG, sex hormone binding globulin; VAT, visceral adipose tissue.

and reducing BMI and abdominal circumference. GLP-1 RAs had similar effects on menstrual frequency, serum total testosterone, free androgen index, SHBG, dehydroepiandrosterone sulfate (DHEA-S), Ferriman-Gallwey scores, androstenedione, LH, fasting blood glucose, fasting insulin, triglycerides, total cholesterol, and blood pressure when compared with metformin.

Effects of GLP1-RA on reproductive endpoints

The effects of liraglutide on ovarian dysfunction in PCOS were evaluated in a double-blind, randomized trial (96). In this study, 72 women with PCOS were allocated to intervention with liraglutide or placebo (1.8 mg/day), in a 2:1 ratio. Bleeding pattern, levels of anti-Müllerian hormone (AMH), sex hormones, and gonadotrophins were assessed and ovarian morphology evaluated. After 26 weeks, liraglutide significantly reduced weight loss by an average of 5.2 kg compared with placebo. The use of liraglutide was also associated with an improvement in bleeding ratio, an increase in SHBG, and a decrease in free testosterone and ovarian volume versus placebo. Contrary to these results, other studies with liraglutide in PCOS found unchanged bleeding frequency despite a decrease in body weight (89–96) and insulin resistance (88). Small sample size, short duration of treatment, and suboptimal liraglutide dose can represent likely explanations for these negative findings.

The impact of liraglutide treatment on pregnancy rates has been seldom investigated. In a randomized, open-label pilot study on 28 women with obesity and PCOS, a 12-week preconception treatment with low-dose liraglutide (1.2 mg daily) in combination with metformin was superior to metformin alone in increasing in vitro fertilization pregnancy rates (97). An increase in the cumulative pregnancy rate was also documented, including spontaneous pregnancies after treatment in women who had been previously been resistant to lifestyle modification and first-line reproductive treatment. Pregnancy rate per embryo transfer was significantly higher in the liraglutide plus metformin group compared to metformin alone (85.7% vs 28.6%, respectively). The cumulative pregnancy rate in a time-frame of 12 months was 69% with the combination therapy compared with 36% in the metformin group.

Natural pregnancy rate was investigated in a clinical trial involving 176 overweight or obese women with PCOS, who were randomized to receive either exenatide 10 μ g twice daily or metformin 1000 mg twice daily for the first 12 weeks. Then all patients were treated with metformin alone during the second 12 weeks (98). During the second 12 weeks, the rate of natural pregnancy of exenatide-treated patients was significantly

higher than metformin-treated patients (43.60% vs 18.70%; $P < 0.05$).

Conclusions

The dramatic increase in obesity and overweight prevalence and its long-term health sequelae are associated with a decline in fertility rates throughout the developed world. The association between excess weight and poor fertility outcomes is indisputable, and weight reduction represents the most significant factor affecting fertility and pregnancy outcomes.

Current experimental and clinical evidence suggests the presence of an underlying pathophysiological link between obesity, GLP-1 kinetic alterations, and PCOS pathogenesis.

Based on the positive results in patients affected by obesity, with or without diabetes, the administration of GLP-1 RA (mainly liraglutide) alone or in combination with metformin has been investigated in women with obesity and PCOS. Several studies demonstrated significant weight loss and testosterone reduction, with mixed results relative to improvements in insulin resistance parameters and menstrual patterns. That being so, the weight loss effects of GLP-1 RA offer a unique opportunity to expand the treatment options available to PCOS patients. This may be extremely useful under some circumstances, such as in assisted reproductive settings when women seeking help for infertility have advanced age and/or poor ovarian reserve. Moreover, these women, being overweight/obese, carry higher risks during controlled ovarian stimulation and throughout pregnancy, which can be minimized by a pretreatment with the specific goal to significantly reduce body weight.

In conclusion, the weight loss effects of GLP-1 RA offer a unique opportunity to expand the treatment options available to PCOS patients. Treatments should be part of a comprehensive, multidisciplinary approach for weight management in women with overweight/obesity and PCOS, and especially in those planning to conceive following assisted reproductive technology. At present, the best strategy starts with comprehensive lifestyle management and may include the use of approved weight loss medications to ameliorate comorbidities and achieve meaningful clinical outcomes.

Acknowledgments

Financial Support: The authors did not receive financial support for the present paper. The editorial assistance was provided by Airon Communication Srl through a Novo Nordisk S.p.A. unconditional grant.

Author Contributions: All the authors contributed to the conception of the work; the acquisition, analysis, and interpretation of data; drafting; and revision of the work. They have read and approved the final version for submission and agree to be personally accountable for their contributions and for ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated, resolved, and documented in the literature.

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Disclosure Summary: The authors have no conflict of interest to disclose.

Data Availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

1. World Health Organization. Obesity and overweight fact sheet. 2016. <http://www.who.int/mediacentre/factsheets/fs311/en/>. Accessed December 19, 2019.
2. Salvestrini V, Sell C, Lorenzini A. Obesity may accelerate the aging process. *Front Endocrinol (Lausanne)*. 2019;10:266.
3. Vurbic D, Harder VS, Redner RR, Lopez AA, Phillips JK, Higgins ST. Co-occurring obesity and smoking among U.S. women of reproductive age: Associations with educational attainment and health biomarkers and outcomes. *Prev Med*. 2015;80:60–66.
4. Ramlau-Hansen CH, Thulstrup AM, Nohr EA, Bonde JP, Sørensen TI, Olsen J. Subfecundity in overweight and obese couples. *Hum Reprod*. 2007;22(6):1634–1637.
5. van der Steeg JW, Steures P, Eijkemans MJ, et al. Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. *Hum Reprod*. 2008;23(2):324–328.
6. Talmor A, Dunphy B. Female obesity and infertility. *Best Pract Res Clin Obstet Gynaecol*. 2015;29(4):498–506.
7. Escobar-Morreale HF. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. *Nat Rev Endocrinol*. 2018;14(5):270–284.
8. Yildiz BO, Bozdag G, Yapici Z, Esinler I, Yarli H. Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria. *Hum Reprod*. 2012;27(10):3067–3073.
9. Yildiz BO. Polycystic ovary syndrome: is obesity a symptom? *Womens Health (Lond)*. 2013;9(6):505–507.
10. Rachoń D, Teede H. Ovarian function and obesity–interrelationship, impact on women's reproductive lifespan and treatment options. *Mol Cell Endocrinol*. 2010;316(2):172–179.
11. Jungheim ES, Moley KH. Current knowledge of obesity's effects in the pre- and periconceptional periods and avenues for future research. *Am J Obstet Gynecol*. 2010;203(6):525–530.
12. Moran LJ, Norman RJ, Teede HJ. Metabolic risk in PCOS: phenotype and adiposity impact. *Trends Endocrinol Metab*. 2015;26(3):136–143.
13. Broughton DE, Moley KH. Obesity and female infertility: potential mediators of obesity's impact. *Fertil Steril*. 2017;107(4):840–847.

14. Wise LA, Rothman KJ, Mikkelsen EM, Sørensen HT, Riis A, Hatch EE. An internet-based prospective study of body size and time-to-pregnancy. *Hum Reprod*. 2010;25(1):253-264.
15. Gesink Law DC, Macle hose RF, Longnecker MP. Obesity and time to pregnancy. *Hum Reprod*. 2007;22(2):414-420.
16. Tamer Erel C, Senturk LM. The impact of body mass index on assisted reproduction. *Curr Opin Obstet Gynecol*. 2009;21(3):228-235.
17. Metwally M, Ong KJ, Ledger WL, Li TC. Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. *Fertil Steril*. 2008;90(3):714-726.
18. Kaye L, Sueldo C, Engmann L, Nulsen J, Benadiva C. Survey assessing obesity policies for assisted reproductive technology in the United States. *Fertil Steril*. 2016;105(3):703-706.e2.
19. Zachariah M, Fleming R, Acharya U. Management of obese women in assisted conception units: a UK survey. *Hum Fertil (Camb)*. 2006;9(2):101-105.
20. American Heart Association; National Heart, Lung, and Blood Institute, Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Executive summary. *Cardiol Rev*. 2005;13(6):322-327.
21. Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2005;90(4):1929-1935.
22. Ehrmann DA, Liljenquist DR, Kasza K, Azziz R, Legro RS, Ghazzi MN; PCOS/Troglitazone Study Group. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2006;91(1):48-53.
23. Glueck CJ, Papanna R, Wang P, Goldenberg N, Sieve-Smith L. Incidence and treatment of metabolic syndrome in newly referred women with confirmed polycystic ovarian syndrome. *Metabolism*. 2003;52(7):908-915.
24. Livshits A, Seidman DS. Fertility issues in women with diabetes. *Womens Health (Lond)*. 2009;5(6):701-707.
25. Iñiguez G, Torrealba IM, Avila A, Cassorla F, Codner E. Adiponectin serum levels and their relationships to androgen concentrations and ovarian volume during puberty in girls with type 1 diabetes mellitus. *Horm Res*. 2008;70(2):112-117.
26. Codner E, Merino PM, Tena-Sempere M. Female reproduction and type 1 diabetes: from mechanisms to clinical findings. *Hum Reprod Update*. 2012;18(5):568-585.
27. Diamanti-Kandarakis E, Piperi C, Korkolopoulou P, et al. Accumulation of dietary glycotoxins in the reproductive system of normal female rats. *J Mol Med (Berl)*. 2007;85(12):1413-1420.
28. Merhi Z. Advanced glycation end products and their relevance in female reproduction. *Hum Reprod*. 2014;29(1):135-145.
29. Dupont J, Reverchon M, Bertoldo MJ, Froment P. Nutritional signals and reproduction. *Mol Cell Endocrinol*. 2014;382(1):527-537.
30. Fontana R, Della Torre S. The Deep Correlation between Energy Metabolism and Reproduction: A View on the Effects of Nutrition for Women Fertility. *Nutrients*. 2016;8(2):87.
31. Jonasson JM, Brismar K, Sparén P, et al. Fertility in women with type 1 diabetes: a population-based cohort study in Sweden. *Diabetes Care*. 2007;30(9):2271-2276.
32. Li X, Ma X. Effects of dyslipidemia on in-vitro fertilization/ intracytoplasmic sperm injection (IVF/ICSI) pregnancy outcome in patients with polycystic ovary syndrome(PCOS). *Fertil Steril*. 2018;110(suppl 4):e198.
33. Mulder CL, Lassi ZS, Grieger JA, et al. Cardio-metabolic risk factors among young infertile women: a systematic review and meta-analysis. *BJOG*. Published online February 12, 2020. doi:10.1111/1471-0528.16171
34. Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. *Hum Reprod*. 1998;13(6):1502-1505.
35. Chavarro JE, Ehrlich S, Colaci DS, et al. Body mass index and short-term weight change in relation to treatment outcomes in women undergoing assisted reproduction. *Fertil Steril*. 2012;98(1):109-116.
36. Kort JD, Winget C, Kim SH, Lathi RB. A retrospective cohort study to evaluate the impact of meaningful weight loss on fertility outcomes in an overweight population with infertility. *Fertil Steril*. 2014;101(5):1400-1403.
37. Sim KA, Dezarnaulds GM, Denyer GS, Skilton MR, Caterson ID. Weight loss improves reproductive outcomes in obese women undergoing fertility treatment: a randomized controlled trial. *Clin Obes*. 2014;4(2):61-68.
38. Mutsaerts MA, van Oers AM, Groen H, et al. Randomized Trial of a Lifestyle Program in Obese Infertile Women. *N Engl J Med*. 2016;374(20):1942-1953.
39. American College of Obstetricians and Gynecologists. Practice bulletin no. 156: Obesity in pregnancy. *Obstet Gynecol*. 2015;126(6):e112-126.
40. Legro RS, Dodson WC, Kris-Etherton PM, et al. Randomized Controlled Trial of Preconception Interventions in Infertile Women With Polycystic Ovary Syndrome. *J Clin Endocrinol Metab*. 2015;100(11):4048-4058.
41. Legro RS, Dodson WC, Kunselman AR, et al. Benefit of Delayed Fertility Therapy With Preconception Weight Loss Over Immediate Therapy in Obese Women With PCOS. *J Clin Endocrinol Metab*. 2016;101(7):2658-2666.
42. De Giuseppe R, Braschi V, Bosoni D, et al. Dietary underreporting in women affected by polycystic ovary syndrome: A pilot study. *Nutr Diet*. 2019;76(5):560-566.
43. Saydam BO, Yildiz BO. Gut-Brain Axis and Metabolism in Polycystic Ovary Syndrome. *Curr Pharm Des*. 2016;22(36):5572-5587.
44. Duca FA, Covasa M. Current and emerging concepts on the role of peripheral signals in the control of food intake and development of obesity. *Br J Nutr*. 2012;108(5):778-793.
45. Morton GJ, Meek TH, Schwartz MW. Neurobiology of food intake in health and disease. *Nat Rev Neurosci*. 2014;15(6):367-378.
46. Ma J, Lin TC, Liu W. Gastrointestinal hormones and polycystic ovary syndrome. *Endocrine*. 2014;47(3):668-678.
47. Hellström PM, Geliebter A, Näslund E, et al. Peripheral and central signals in the control of eating in normal, obese and binge-eating human subjects. *Br J Nutr*. 2004;92 Suppl 1:S47-S57.
48. English PJ, Ghatei MA, Malik IA, Bloom SR, Wilding JP. Food fails to suppress ghrelin levels in obese humans. *J Clin Endocrinol Metab*. 2002;87(6):2984.
49. Tschöp M, Weyer C, Tataranni PA, Devanarayan V, Ravussin E, Heiman ML. Circulating ghrelin levels are decreased in human obesity. *Diabetes*. 2001;50(4):707-709.
50. Zwirska-Korczala K, Konturek SJ, Sodowski M, et al. Basal and postprandial plasma levels of PYY, ghrelin, cholecystokinin, gastrin and insulin in women with moderate and morbid obesity and metabolic syndrome. *J Physiol Pharmacol*. 2007;58(Suppl 1):S13-S35.
51. Gao T, Wu L, Chang F, Cao G. Low circulating ghrelin levels in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Endocr J*. 2016;63(1):93-100.
52. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology*. 2007;132(6):2131-2157.
53. Rocca AS, Brubaker PL. Role of the vagus nerve in mediating proximal nutrient-induced glucagon-like peptide-1 secretion. *Endocrinology*. 1999;140(4):1687-1694.
54. Abbott CR, Monteiro M, Small CJ, et al. The inhibitory effects of peripheral administration of peptide YY(3-36) and glucagon-like peptide-1 on food intake are attenuated by

- ablation of the vagal-brainstem-hypothalamic pathway. *Brain Res.* 2005;1044(1):127-131.
55. Nauck MA, Niedereichholz U, Ettler R, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. *Am J Physiol.* 1997;273(5):E981-E988.
 56. Göke R, Larsen PJ, Mikkelsen JD, Sheikh SP. Distribution of GLP-1 binding sites in the rat brain: evidence that exendin-4 is a ligand of brain GLP-1 binding sites. *Eur J Neurosci.* 1995;7(11):2294-2300.
 57. Larsen PJ. Mechanisms behind GLP-1 induced weight loss. *Br J Diabetes Vasc Dis.* 2008;8(Suppl 2):S34-S41.
 58. Verdich C, Flint A, Gutzwiller JP, et al. A meta-analysis of the effect of glucagon-like peptide-1 (7-36) amide on ad libitum energy intake in humans. *J Clin Endocrinol Metab.* 2001;86(9):4382-4389.
 59. Knop FK, Aaboe K, Vilsbøll T, et al. Impaired incretin effect and fasting hyperglucagonaemia characterizing type 2 diabetic subjects are early signs of dysmetabolism in obesity. *Diabetes Obes Metab.* 2012;14(6):500-510.
 60. Buhmann H, le Roux CW, Bueter M. The gut-brain axis in obesity. *Best Pract Res Clin Gastroenterol.* 2014;28(4):559-571.
 61. Muscelli E, Mari A, Casolaro A, et al. Separate impact of obesity and glucose tolerance on the incretin effect in normal subjects and type 2 diabetic patients. *Diabetes.* 2008;57(5):1340-1348.
 62. Galindo Muñoz JS, Jiménez Rodríguez D, Hernández Morante JJ. Diurnal rhythms of plasma GLP-1 levels in normal and overweight/obese subjects: lack of effect of weight loss. *J Physiol Biochem.* 2015;71(1):17-28.
 63. Carr RD, Larsen MO, Jelic K, et al. Secretion and dipeptidyl peptidase-4-mediated metabolism of incretin hormones after a mixed meal or glucose ingestion in obese compared to lean, nondiabetic men. *J Clin Endocrinol Metab.* 2010;95(2):872-878.
 64. Ranganath LR, Beety JM, Morgan LM, Wright JW, Howland R, Marks V. Attenuated GLP-1 secretion in obesity: cause or consequence? *Gut.* 1996;38(6):916-919.
 65. Verdich C, Toubro S, Buemann B, Lysegård Madsen J, Juul Holst J, Astrup A. The role of postprandial releases of insulin and incretin hormones in meal-induced satiety—effect of obesity and weight reduction. *Int J Obes Relat Metab Disord.* 2001;25(8):1206-1214.
 66. Vrbikova J, Hill M, Bendlova B, et al. Incretin levels in polycystic ovary syndrome. *Eur J Endocrinol.* 2008;159(2):121-127.
 67. Arusoglu G, Koksak G, Cinar N, Tapan S, Aksoy DY, Yildiz BO. Basal and meal-stimulated ghrelin, PYY, CCK levels and satiety in lean women with polycystic ovary syndrome: effect of low-dose oral contraceptive. *J Clin Endocrinol Metab.* 2013;98(11):4475-4482.
 68. Moran LJ, Noakes M, Clifton PM, et al. Postprandial ghrelin, cholecystokinin, peptide YY, and appetite before and after weight loss in overweight women with and without polycystic ovary syndrome. *Am J Clin Nutr.* 2007;86(6):1603-1610.
 69. Lin T, Li S, Xu H, et al. Gastrointestinal hormone secretion in women with polycystic ovary syndrome: an observational study. *Hum Reprod.* 2015;30(11):2639-2644.
 70. Tsilchorozidou T, Batterham RL, Conway GS. Metformin increases fasting plasma peptide tyrosine tyrosine (PYY) in women with polycystic ovarian syndrome (PCOS). *Clin Endocrinol (Oxf).* 2008;69(6):936-942.
 71. Lim SS, Hutchison SK, Van Ryswyk E, Norman RJ, Teede HJ, Moran LJ. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database Syst Rev.* 2019;3:CD007506.
 72. Haqq L, McFarlane J, Dieberg G, Smart N. Effect of lifestyle intervention on the reproductive endocrine profile in women with polycystic ovarian syndrome: a systematic review and meta-analysis. *Endocr Connect.* 2014;3(1):36-46.
 73. Thomson RL, Buckley JD, Noakes M, Clifton PM, Norman RJ, Brinkworth GD. The effect of a hypocaloric diet with and without exercise training on body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2008;93(9):3373-3380.
 74. Drucker DJ. Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1. *Cell Metab.* 2018;27(4):740-756.
 75. Wang B, Zhong J, Lin H, et al. Blood pressure-lowering effects of GLP-1 receptor agonists exenatide and liraglutide: a meta-analysis of clinical trials. *Diabetes Obes Metab.* 2013;15(8):737-749.
 76. van Genugten RE, Möller-Goede DL, van Raalte DH, Diamant M. Extra-pancreatic effects of incretin-based therapies: potential benefit for cardiovascular-risk management in type 2 diabetes. *Diabetes Obes Metab.* 2013;15(7):593-606.
 77. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med.* 2016;375(19):1834-1844.
 78. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2016;375(4):311-322.
 79. Astrup A, Rössner S, Van Gaal L, et al.; NN8022-1807 Study Group. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet.* 2009;374(9701):1606-1616.
 80. Astrup A, Carraro R, Finer N, et al.; NN8022-1807 Investigators. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int J Obes (Lond).* 2012;36(6):843-854.
 81. Wadden TA, Hollander P, Klein S, et al.; NN8022-1923 Investigators. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes (Lond).* 2013;37(11):1443-1451.
 82. Pi-Sunyer X, Astrup A, Fujioka K, et al.; SCALE Obesity and Prediabetes NN8022-1839 Study Group. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *N Engl J Med.* 2015;373(1):11-22.
 83. Davies MJ, Bergenstal R, Bode B, et al.; NN8022-1922 Study Group. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial. *Jama.* 2015;314(7):687-699.
 84. Blackman A, Foster GD, Zammit G, et al. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. *Int J Obes (Lond).* 2016;40(8):1310-1319.
 85. Singh AK, Singh R. Pharmacotherapy in obesity: a systematic review and meta-analysis of randomized controlled trials of anti-obesity drugs. *Expert Rev Clin Pharmacol.* 2020;13(1):53-64.
 86. Elkind-Hirsch K, Marrioneaux O, Bhushan M, Vernor D, Bhushan R. Comparison of single and combined treatment with exenatide and metformin on menstrual cyclicity in overweight women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2008;93(7):2670-2678.
 87. Rasmussen CB, Lindenberg S. The effect of liraglutide on weight loss in women with polycystic ovary syndrome: an observational study. *Front Endocrinol (Lausanne).* 2014;5:140.
 88. Kahal H, Aburima A, Ungvari T, et al. The effects of treatment with liraglutide on atherothrombotic risk in obese young women with polycystic ovary syndrome and controls. *BMC Endocr Disord.* 2015;15:14.
 89. Jensterle M, Salamun V, Kocjan T, Vrtacnik Bokal E, Janez A. Short term monotherapy with GLP-1 receptor agonist liraglutide or PDE 4 inhibitor roflumilast is superior to metformin in weight loss in obese PCOS women: a pilot randomized study. *J Ovarian Res.* 2015;8:32.
 90. Frössing S, Nylander M, Chabanova E, et al. Effect of liraglutide on ectopic fat in polycystic ovary syndrome: A randomized clinical trial. *Diabetes Obes Metab.* 2018;20(1):215-218.

91. Jensterle Sever M, Kocjan T, Pfeifer M, Kravos NA, Janez A. Short-term combined treatment with liraglutide and metformin leads to significant weight loss in obese women with polycystic ovary syndrome and previous poor response to metformin. *Eur J Endocrinol*. 2014;170(3):451-459.
92. Jensterle M, Kravos NA, Pfeifer M, Kocjan T, Janez A. A 12-week treatment with the long-acting glucagon-like peptide 1 receptor agonist liraglutide leads to significant weight loss in a subset of obese women with newly diagnosed polycystic ovary syndrome. *Hormones (Athens)*. 2015;14(1):81-90.
93. Niafar M, Pourafkari L, Porhomayon J, Nader N. A systematic review of GLP-1 agonists on the metabolic syndrome in women with polycystic ovaries. *Arch Gynecol Obstet*. 2016;293(3):509-515.
94. Jensterle M, Kravos NA, Goričar K, Janez A. Short-term effectiveness of low dose liraglutide in combination with metformin versus high dose liraglutide alone in treatment of obese PCOS: randomized trial. *BMC Endocr Disord*. 2017;17(1):5.
95. Han Y, Li Y, He B. GLP-1 receptor agonists versus metformin in PCOS: a systematic review and meta-analysis. *Reprod Biomed Online*. 2019;39(2):332-342.
96. Nylander M, Frössing S, Clausen HV, Kistorp C, Faber J, Skouby SO. Effects of liraglutide on ovarian dysfunction in polycystic ovary syndrome: a randomized clinical trial. *Reprod Biomed Online*. 2017;35(1):121-127.
97. Salamun V, Jensterle M, Janez A, Vrtacnik Bokal E. Liraglutide increases IVF pregnancy rates in obese PCOS women with poor response to first-line reproductive treatments: a pilot randomized study. *Eur J Endocrinol*. 2018;179(1):1-11.
98. Liu X, Zhang Y, Zheng SY, et al. Efficacy of exenatide on weight loss, metabolic parameters and pregnancy in overweight/obese polycystic ovary syndrome. *Clin Endocrinol (Oxf)*. 2017;87(6):767-774.