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Effects of liraglutide on ovarian dysfunction in polycystic ovary syndrome: a randomized clinical trial

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KEY MESSAGE

In this double-blind, placebo-controlled, randomized trial, the glucagonlike peptide-1 analogue liraglutide was found to ameliorate ovarian dysfunction in overweight women with PCOS. Improved bleeding regularity, reduced levels of free testosterone and substantial weight loss were observed. Liraglutide could serve as a treatment in overweight women with PCOS.

A B S T R A C T

Polycystic ovary syndrome (PCOS) encompasses ovarian and metabolic dysfunction. Glucagon-like peptide-1 (GLP-1) analogues facilitate weight loss and ameliorate metabolic dysfunction in overweight women with PCOS, but their effect on ovarian dysfunction is scarcely reported. In a double-blind, randomized trial, 72 women with PCOS were allocated to intervention with the GLP-1 analogue liraglutide or placebo (1.8 mg/day), in a 2:1 ratio. At baseline and 26-week follow-up, bleeding pattern, levels of AMH, sex hormones and gonadotrophins were assessed and ovarian morphology evaluated. Liraglutide caused 5.2 kg (95% CI 3.0 to 7.5, $P < 0.0001$) weight loss versus placebo. Bleeding ratio improved with liraglutide: 0.28 (95% CI 0.20 to 0.36, $P < 0.001$); placebo: 0.14 (95% CI 0.02 to 0.26, $P < 0.05$); between-group difference: 0.14 (95% CI 0.03 to 0.24, $P < 0.05$). In the liraglutide group, SHBG increased by 7.4 nmol/L (95% CI 4.1 to 10.7) and free testosterone decreased by 0.005 nmol/L (95% CI −0.009 to −0.001). Ovarian volume decreased by −1.6 ml (95% CI −3.3 to 0.1) with liraglutide versus placebo. Nausea and constipation were more prevalent in the liraglutide group. Liraglutide improved markers of ovarian function in overweight women with PCOS, and might be a possible alternative intervention.

Introduction

With a prevalence of 10%, polycystic ovary syndrome (PCOS) is a common endocrine disorder in premenopausal women (Bozdag et al., 2016). The syndrome has a complex pathophysiology with two main issues: a metabolic and an ovarian dysfunction, seen isolated or simultaneously (Dunaif and Fauser, 2013). Central for PCOS is the ovarian dysfunction, clinically seen as oligoovlation, anovulation, androgen excess and polycystic ovarian morphology. These represent the Rotterdam criteria upon which

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the PCOS diagnosis is based (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004).

Folliculogenesis is a highly complex process directed by autocrine, paracrine and endocrine factors, e.g. gonadotrophins, sex steroids and anti-Müllerian hormone (AMH) (Dewailly et al., 2016). The glycoprotein AMH is produced by the granulosa cells of early developing follicles (Pellatt et al., 2007). By inhibiting follicular recruitment and FSH-dependent follicular growth, AMH is thought to have a protective effect on the ovarian reserve in the healthy individual (Dumont et al., 2015). As a result of a large pool of early developing follicles and greater AMH production per follicle, women with PCOS have higher AMH levels than controls (Pellatt et al., 2007; Piouka et al., 2009). Here, the protective mechanism goes beyond its physiological purpose, causing 'follicular arrest' and anovulation (Dumont et al., 2015). In overweight women with PCOS, weight loss recovers the arrested folliculogenesis, seen as improved bleeding pattern (Nybacka et al., 2013), whereas metformin, possibly through increased insulin sensitivity, improves cycle regularity in both overweignt and normal weight women with PCOS (Romualdi et al., 2010, 2011). Indeed, insulin is a central factor in PCOS, in which intrinsic and obesity-related insulin resistance causes compensatory hyperinsulinaemia. Insulin amplifies the excessive LH-stimulated ovarian androgen production (Tosi et al., 2012) and decreases the hepatic sex hormone-binding globulin (SHBG) production, ultimately causing hyperandrogenism (Nestler et al., 1991).

The ideal PCOS treatment addresses both the metabolic and the ovarian dysfunction of the syndrome. Over the past decade, glucagon-like peptide 1 (GLP-1) analogues are increasingly used in treating type 2 diabetes and obesity, where they mimic the effect of the endogenous incretin hormone, promoting weight loss, improved glycaemic control and reduced dyslipidaemia (Vilsbøll et al., 2012). Because of the resemblance between type 2 diabetes and PCOS, and the fact that metformin affects ovarian dysfunction, GLP-1 analogues might have a role in treating the syndrome. The GLP-1 analogue liraglutide has been found to cause weight loss in several small trials on women with PCOS (Jensterle et al., 2015a, 2015b, 2015c; Kahal et al., 2015), but results on bleeding frequency are sparse. Losing weight and maintaining a stable body weight is difficult, and interventions effectively treating both the body weight and the ovarian dysfunction are warranted.

We hypothesized that intervention with a GLP-1 analogue would improve ovarian dysfunction in overweight women with PCOS, possibly through weight loss and altered glucose metabolism. In this randomized, clinical trial, we aimed to investigate the effect of liraglutide in women with PCOS on markers of ovarian dysfunction: bleeding ratio, ovarian morphology, levels of AMH and androgens.

Materials and methods

Protocol and ethics

This was an investigator-initiated, double blind, placebo-controlled, randomized trial, conducted between March 2014 and December 2015 at Herlev Gentofte Hospital, University of Copenhagen, Denmark. The study was approved by the regional Ethics Committee of the Capital Region of Denmark (ID: H-2-2013-142), the Danish Health Authority (EudraCT: 2013-003862-15) and the Danish Data Protection Agency. The study was conducted in accordance with Good Clinical Practice guidelines and the declaration of Helsinki and registered at www.clinicaltrials.gov (NCT02073929). Oral and written consent were obtained for each participant before inclusion. The protocol has been published elsewhere (Frøssing et al., 2015). At baseline and 26-week follow-up, anthropometrics and Ferriman-Gallway score were assessed, blood tests, a 75 g oral glucose tolerance test and a transvaginal ultrasound were conducted. Blood was drawn between 8.00 and 10.00 am after overnight fasting. Blood for determination of AMH and insulin levels was centrifuged and serum was stored at –80°C until analysis.

Population

In Denmark, women with PCOS are usually managed by a general practitioner or a private-practising gynaecologist, rather than in hospital. Because of this, women were mainly recruited from social media (www.facebook.com/PCOSkliniskforsoeg), from advertising in the local area and from general practitioners or private gynaecologists, but also from our outpatient clinic. Briefly, inclusion criteria were as follows: age over 18 years, PCOS according to Rotterdam criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004), body mass index 25 kg/m^2 or more, insulin resistance (defined as fasting plasma C-peptide >600 pmol/L), or both. Irregular bleeding was defined as cycle length more than 35 days and hyperandrogenism as total testosterone above reference levels, free testosterone above reference level (1.80 nmol/l and 0.0034 nmol/l, respectively), Ferriman-Gallway score 8 or over, or all three. In brief, exclusion criteria were pregnancy, diabetes, use of hormonal contraceptives (within 6 weeks before inclusion), anti-diabetic, anti-androgenic agents, or both (within 3 months before inclusion). Other causes of irregular menstruation and androgen excess, e.g. hyperprolactinaemia, thyroid and adrenal diseases, were excluded, using biochemical work-up performed at screening. As pregnancy was an exclusion criterion, participants had a copper intrauterine device inserted at the baseline visit. In case of contraindications, the participant was instructed in concomitant use of diaphragm and condom, in accordance with guidelines from the Danish Health Authority. A pregnancy test was carried out at every visit.

Randomization and intervention

Women were randomized to 26 weeks of intervention with liraglutide or placebo in a 2:1 ratio, in blocks of six. Novo Nordisk A/S, Bagsværd, Denmark, provided identically packed and labelled study drug (liraglutide and placebo) as well as a randomization list. All participants and investigators were blinded as an independent secretary handled the randomization list and instructed the investigators in which serial numbers, i.e. drug packages, to be handed out to each participant. The study drug was administered subcutaneously 1.8 mg/day, starting at 0.6 mg/day and 1.2 mg/day for the first and second week, respectively.

Outcomes

Pre-specified outcomes included the between-group difference in bleeding ratio at follow-up, as well as the between-group differences in change (from baseline to follow-up) in bleeding ratio, ovarian volume, stromal volume, antral follicle count, Ferriman-Gallway score, serum levels of AMH, SHBG and androgens.

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