The FSRH has received several member enquiries relating to GLP-1 agonists and contraception. Given the evidence is very limited, an expert group is being convened to agree recommendations.

In the interim, the FSRH Clinical Effectiveness Unit (CEU) have reviewed the position and suggest following the guidance set out in the SmPC and BNF, which is summarised in the members evidence response below.

Question

What advice should we give to patients about oral contraceptives when taking the GLP-1 agonists tirzepatide or semaglutide?

Response

Tirzepatide (Mounjaro®)

The BNF describes tirzepatide as a long-acting GIP (glucose-dependent insulinotropic polypeptide) receptor and GLP-1 (glucagon-like peptide-1) receptor agonist that increases insulin sensitivity and secretion, suppresses glucagon secretion, and slows gastric emptying (1). The BNF (1) and Summary of Product Characteristics (SmPC) for tirzepatide (mounjaro®) (2) advise that '*female patients who are overweight or obese and using an oral contraceptive should add a barrier method of contraception or switch to a non-oral contraceptive method for the first 4 weeks of treatment, and for 4 weeks after each dose increase*.' The BNF also advise that tirzepatide is avoided during pregnancy and that treatment is discontinued at least one month before a planned pregnancy. (1)

The evidence

A literature search by the CEU identified one review paper by Skelley et al (2024) (3) that described a single clinical trial (4) on the effect of tirzepatide on oral contraceptives. The tirzepatide study included 40 women with a BMI≥18.5 kg/m^2 who had a single dose of 5mg tirzepatide injection alongside 0.25mg norgestimate (NGM) and 0.035mg ethinyl estradiol (EE). The area under the curve (AUC), which reflects the actual body exposure to a drug after administration, was statistically significantly reduced by 20% for EE and 21% for NGM. The peak concentration of the drug in the bloodstream and elsewhere in the body (Cmax), was reduced by 59% for EE and 66% for NGM. In addition, the time to maximum plasma concentration (Tmax) was reduced (by 2.5 to 4.5 hours). The review authors considered these effects to be clinically relevant.

Semaglutide (Ozempic® and Wegovy®) sho

The BNF describes the action of semaglutide as binding to, and activating, the GLP-1 receptor to increase insulin secretion, suppress glucagon secretion and slow gastric emptying (5). The SmPC for both Ozempic® (6) and Wegovy® (7) mention that '*Semaglutide is not anticipated to decrease the effect of oral contraceptives as semaglutide did not change the overall exposure of ethinylestradiol and levonorgestrel to a clinically relevant degree when an oral contraceptive combination medicinal product (0.03 mg ethinylestradiol/0.15 mg levonorgestrel) was co-administered with semaglutide.'* The BNF also advise that semaglutide is avoided during pregnancy and that effective contraception is used during and for at least two months after stopping treatment. (5)

The evidence

The review paper by Skelley (3) includes one study of oral semaglutide (8) and one of subcutaneous semaglutide (9). In the cross-over trial of oral semaglutide (3 mg for 1 weeks, 7 mg for 1 week, 14 mg for 4 weeks), which included 25 postmenopausal women with a BMI of 20-29.9kg/mg^2, no effect was seen on the AUC, Cmax or Tmax in relation to the oral contraceptive (0.15mg LNG + 0.03mg EE). For the cross-over study of subcutaneous semaglutide (0.25 mg for 4 weeks, 0.5mg for 4 weeks, 1 mg for 5 weeks), 39 women took 0.15 mg LNG and 0.03 mg EE (given 8 days before and during the last week of semaglutide dosing). There was no effect on the AUC for EE, but the LNG AUC was 20% higher during semaglutide treatment (not clinically relevant). There was no effect on Cmax for either LNG or EE. Tmax was not delayed for LNG and was delayed by 1 hour for EE, which was not thought to have a clinically relevant impact.

Gastrointestinal adverse reactions

The SmPC for Mounjaro® (2) lists diarrhoea and vomiting as very common adverse reactions (≥1/10), based on the frequency reported in clinical trials supporting the weight management indication. The incidence of nausea, vomiting, and diarrhoea was higher during the dose escalation period and decreased over time. The SmPC for Ozempic® (6) mentions that diarrhoea is a very common (≥1/10) adverse reaction associated with semaglutide, and vomiting is listed as a common adverse reaction (≥1/100). For Wegovy®, the SmPC (7) mentions both vomiting and diarrhoea as very common adverse reactions (≥1/10), mainly seen in the dose-escalation period.

Conclusion

From the evidence identified, tirzepatide appears to reduce the absorption of oral contraceptives. As advised in the BNF and SmPC, **those who are overweight or obese and taking tirzepatide should either use a non-oral contraceptive method (for example, LARC methods, combined hormonal vaginal ring or patch) or, if using oral contraception add a barrier method for 4 weeks after starting tirzepatide, and for 4**

weeks after each dose increase. The impact of semaglutide on oral contraceptive absorption does not appear to be clinically significant.

In addition to the direct evidence, an important consideration is the likelihood of diarrhoea and vomiting as a potential side effect, which could affect exposure to contraceptive hormones through reduced absorption. In the case of diarrhoea or vomiting during use of oral contraception, the following FSRH recommendations should be followed, as per 'Drug Interactions with Hormonal Contraception' (10).

Follow missed pill rules if vomiting occurs within a few hours of pill taking (see manufacturer instructions) or if severe diarrhoea persists for >24 hours

If an individual has persistent vomiting or diarrhoea, consider non-oral contraception

Consistent use of condoms is recommended