FSRH The Faculty of Sexual & Reproductive Healthcare

FSRH statement: Glucagon-like peptide-1 (GLP-1) agonists and oral contraception

FSRH recommendations

- **Individuals should be advised to use contraception whilst using GLP-1 agonists.**
- **Individuals using tirzepatide and oral contraception should switch to a non-oral contraceptive method, or add a barrier method of contraception, for four weeks after initiation and for four weeks after each dose increase.**
- **There is no need to add a barrier method of contraception when using semaglutide, dulaglutide, exenatide, lixisenatide or liraglutide.**
- **Individuals who experience severe diarrhoea or vomiting during use of GLP-1 agonists should follow existing FSRH recommendations.**

GLP-1 agonists

The GLP-1 agonists (semaglutide, exenatide, liraglutide, dulaglutide, lixisenatide) bind to and activate the GLP-1 receptor to increase insulin secretion, supress glucagon secretion and slow gastric emptying. Tirzepatide is a long-acting glucose-dependent insulinotropic polypeptide receptor and GLP-1 receptor agonist that increases insulin sensitivity and secretion, suppresses glucagon secretion, and slows gastric emptying. GLP-1 agonists are indicated for type two diabetes and weight management. The British National Formulary advises that GLP-1 agonists are avoided during pregnancy and that women of childbearing age use effective contraception whilst using GLP-1 agonists.[1,2,3,4,5,6].

The evidence

The evidence for all GLP-1 agonists is limited to pharmacokinetic studies. Detailed evidence for each GLP-1 agonist can be found in appendix 1. Tirzepatide is the only GLP-1 agonist found to have a clinically significant effect on the bioavailability of oral contraceptives. No clinically relevant reduction in bioavailability of oral contraceptives has been observed with semaglutide, exenatide, liraglutide, dulaglutide or lixisenatide.

Side effects

The SmPCs for all GLP-1 agonists mention diarrhoea and vomiting as either very common (≥1/10) or common (≥1/100) adverse reactions[7,8,9,10,11,12,13]. This is reported to be more common during the dose escalation period for tirzepatide[7] and semaglutide[9,] and specified to reduce over time for exenatide[11] and dulaglutide[12]. Diarrhoea and vomiting could affect absorption of oral contraceptives which in turn may reduce effectiveness. Individuals who

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experience severe diarrhoea or vomiting whilst using GLP-1 agonists and oral contraception should follow FSRH recommendations:[14]

- 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

Emergency contraception

There is no direct evidence or pharmacokinetic data regarding the effect of GLP-1 agonists on emergency hormonal contraception. The copper intrauterine device is the most effective method of emergency contraception and should always be offered where appropriate. As per current FSRH recommendations[15], double dose LNG-EC should be considered in individuals with a BMI over 26kg/m^2 or weight over 70kg.

Preconception advice

There is a lack of safety data available for use of GLP-1 agonists in pregnancy. Individuals should be advised to use contraception during use of all GLP-1 agonists and informed of the recommended 'washout' period (i.e. the recommended duration between discontinuation of the GLP-1 agonist prior to a planned pregnancy.)

GLP-agonist	Washout period
Tirzepatide	One month[6]
Semaglutide	Two months[1]
Exenatide	12 weeks[2]

Table 1. Washout periods of GLP-1 agonists

Patient information

An information leaflet, produced by the FSRH CEU can be found here.

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Appendix 1

The CEU searched for evidence on all GLP-1 agonists and their effect on hormonal contraception and found limited data from small pharmacokinetic studies.

Explanation of terms:

- The area under the time curve during one dosing interval (AUC) reflects the actual body exposure to a drug after administration[16].
- Cmax is the peak concentration of the drug in the bloodstream and elsewhere in the body. A decrease in Cmax beyond a critical concentration can reduce the efficacy of the drug[16].
- Tmax is the time to maximum plasma concentration. An increase in Tmax means that it takes longer to reach peak concentration, which could delay absorption of the contraceptive[16].

Tirzepatide

A review paper by Skelley et al 2024[16] described a single clinical trial[17] 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 AUC was statistically significantly reduced by 20% for EE and 21% for NGM. Cmax was reduced by 59% for EE and 66% for NGM. In addition, Tmax was increased from 2.5 to 4.5 hours. The review authors considered these effects to be clinically relevant.

Semaglutide

In a cross-over trial of oral semaglutide[18], including 25 postmenopausal women with a BMI 20-29.9kg/mg^2, no effect was seen on the AUC, Cmax or Tmax in relation to the oral contraceptive (0.15mg levonorgestrel (LNG) + 0.03mg EE). For the cross-over study of subcutaneous semaglutide[19], 39 women took 0.15 mg LNG and 0.03 mg EE (given eight 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 one hour for EE, which was not thought to have a clinically relevant impact.

Exenatide

A trial[20] including 32 women found that exenatide did not alter the bioavailability nor decrease the lowest daily concentrations for either oral contraceptive component (EE 30 µg, LNG 150 µg). No substantive changes in oral contraceptive pharmacokinetics occurred when oral contraceptive was administered one hour before exenatide. Single-dose oral contraceptive administration 30 minutes after exenatide resulted in mean Cmax reductions of 46% and 41% for EE and LNG, respectively. Repeated daily oral contraceptive administration 30 minutes after exenatide resulted in Cmax reductions of 45% and 27% for EE and LNG, respectively. Peak oral contraceptive concentrations were delayed approximately three to four hours. The study authors concluded that the observed reduction in Cmax is likely of limited importance

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given the unaltered oral contraceptive bioavailability and trough concentrations; however, as contraceptive efficacy is dependent on threshold concentrations, patients should be advised to take those drugs at least one hour before exenatide injection.

Liraglutide

A pharmacokinetic study[21] including 21 postmenopausal women found no significant difference in AUC when EE was compared with placebo. When used with liraglutide, the AUC for levonorgestrel was 18% greater than when used with placebo. However, the study still demonstrated that LNG levels were comparable when used with either liraglutide or placebo by using a slightly different measure (observed exposure to a drug)[22]. The Cmax values for EE and LNG were 12% and 13% lower with liraglutide respectively, when compared to placebo. Both EE and LNG reached Cmax approximately 1.5 hours later with liraglutide. No clinically relevant reduction in bioavailability of EE /LNG was observed. The effect of liraglutide on gastric emptying decreases over time, owing to tolerance development resulting from continuous activation of the GLP-1 receptor[23].

Dulaglutide

A 2017 review article[24] looked at the effect of dulaglutide on various drugs, including oral contraception as reported in four clinical pharmacology studies. Dulaglutide did not affect the absorption of the tested medications to a clinically relevant degree. Based on the pharmacokinetic and pharmacodynamic evaluations, no dose adjustments for Ortho-Cyclen® (EE and norgestimate) were recommended when coadministered with dulaglutide.

Lixisenatide

A literature search did not identify any evidence for lixisenatide. The lixisenatide SmPC[13] describes the Cmax, Tmax and AUC of EE and LNG as unchanged when an oral contraceptive was given one hour before or 11 hours after 10 mcg lixisenatide. When the oral contraceptive was given one hour before or four hours after lixisenatide, there was no change to the AUC. Cmax of EE and LNG was decreased and median T max delayed, but not to a clinically relevant degree and no dose adjustment for oral contraceptives is required.

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