The specialist authority for menopause & post reproductive health

Use of incretin-based therapies in women using hormone replacement therapy (HRT)

Introduction

Incretin-based therapies refers to a class of medications used for the treatment of diabetes and obesity that mimic the action of incretins — "gut hormones" that regulate insulin secretion, appetite and satiety, amongst other functions.

This BMS Tool for Clinicians will clarify:

- Background information about obesity and diabetes, the primary disease indications for incretin-based therapies
- Indications for the use of incretin-based therapies
- Considerations when prescribing incretin-based therapies in women using HRT during the menopause transition and post-menopause
- General guidance

This Tool for Clinicians will not cover all the effects of incretin-based therapies or their potential effects if used outside regulator approved indications.

Background

Rates of obesity have more than trebled in the UK over the last 30 years in line with the worldwide obesity epidemic[1]. Complex environmental factors contribute to this increase and the World Health Organisation has shifted the focus from individual to societal causes.

According to NHS digital data from 2022, the proportion of overweight and obesity combined among women aged 45 to 54 was 64%, with the rate of obesity being 34%. Rates among women aged 55 to 64 were 69% and 35%, respectively.

Obesity is associated with significant morbidity and mortality[2]. It is positively associated with cardiovascular disease (CVD), hypertension, pre-diabetes, type 2 diabetes (T2D), hyperlipidaemia, metabolic-dysfunction associated steatotic liver disease (MASLD), chronic kidney disease, several cancers including breast, endometrial and colon cancer, osteoarthritis, sleep apnoea, other respiratory problems and gallbladder disease[3].

The menopause transition results in an average positive energy balance of 2-3 kg, leading to central weight gain and increased metabolic dysfunction[4]. Hormonal changes during the menopause transition are associated with increases in waist circumference and central abdominal (visceral) fat both in women with or without obesity. These changes are being amplified by the obesity epidemic[1].

'Overweight' is defined as body mass index (BMI) 25-29.9 kg/m^2. 'Obesity' is traditionally defined as a BMI over 30 kg/m^2, with lower ethnicity-specific cut-offs in South Asian, Chinese, Arab and Black populations. However, BMI alone is not a reliable marker of cardiometabolic risk[5]. Accumulating data suggests that the distribution of adipose tissue is a key factor contributing to cardiometabolic risk[6,7]. Women with central distribution of obesity, reflecting visceral fat accumulation, carry a higher cardiometabolic risk compared with women who have a favourable waist/hip ratio[6].

The rates of endometrial hyperplasia, cancer and death from endometrial cancer are increasing in women with obesity[8]. Weight loss has been shown to improve response rates in women with obesity and atypical hyperplasia or low-risk endometrial cancer undergoing conservative management with intrauterine progestogen[9].

The prevalence of T2D is also increasing[10,11]. Rates increase with age and menopause status. In 2019, 4.8 million people in the UK were diagnosed with diabetes (90% with T2D). T2D is associated with an increased risk of developing CVD, dementia, breast cancer, endometrial cancer and also increased fracture risk. People living with T2D are 50% more likely to die prematurely.

There is widespread recognition of the need for medications for obesity to help suitable individuals achieve successful weight loss, reducing chronic disease risk in people with obesity[6]. The family of incretin-based therapies including glucagon-like peptide-1 receptor agonists (GLP-1RAs) such as semaglutide, and the dual glucagon-like peptide-1 and glucose-dependent insulinotropic peptide agonist tirzepatide, are widely used in the treatment of diabetes and/or obesity.

This Tool for Clinicians will focus on semaglutide and tirzepatide but the general principles apply broadly to products from these classes of incretin-based therapies.

Indications for use of incretin-based therapies

In the UK, the most effective medications currently approved and used for treatment of obesity are semaglutide and tirzepatide, delivered as once weekly subcutaneous injections. These medications result in significantly greater weight loss compared with placebo[12,13] and improvement in HbA1c in patient with diabetes[14]. Use of tirzepatide and semaglutide in patients with obesity and advanced cardiac disease have demonstrated improved health outcomes, including improved survival, compared with placebo[15-17].

The current licensing regulator approved indications for semaglutide and tirzepatide are:

- BMI ≥ 30 kg/m^2 (obesity) or
- ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus)

and:

- for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:
  — as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
  — in addition to other medicinal products for the treatment of diabetes

In practice however, NHS prescribing recommendations by the National Institute for Health and Care Excellence (NICE) advise more stringent criteria[18,19].

Recognised adverse events of incretin-based therapies include common gastrointestinal side effects and less common but more serious risks such as gallbladder disorders, acute pancreatitis and acute intestinal obstruction, usually in individuals with pre-existing risk factors. The manufacturers also include product warning of a theoretical risk of medullary thyroid cancer; they are thus contraindicated in people with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia. Overall risks of significant events, including cardiovascular endpoints and severe hypoglycaemia, with both drugs are low[14].

Considerations when prescribing semaglutide or tirzepatide in women using HRT during the menopause transition

As obesity and diabetes increase the risk of venous thromboembolism (VTE), transdermal delivery of estrogen is preferred as this is neutral to VTE risk[20], whereas oral estrogen increases VTE risk[21]. Transdermal estrogen absorption is unaffected by concomitant oral medications. If treatment with incretin-based therapies is proposed in a woman using oral estrogen-based HRT, consideration should be given to switching to transdermal-estrogen based HRT.

The primary consideration in relation to women using combined HRT for treatment of menopause symptoms while receiving semaglutide or tirzepatide to treat diabetes or obesity therefore relates to concerns over endometrial protection from potentially reduced absorption of oral progestogens.

Semaglutide and tirzepatide result in delayed gastric emptying and gastrointestinal side effects are common. The impact of these medications on efficacy of co-prescribed oral hormone medications within HRT are unknown. The effect on absorption and bioavailability of combination oral contraceptive (COC) varies by incretin-based products. Reduced bioavailability is seen with tirzepatide[22]. Semaglutide may confer similar effects through its effects on gastric emptying, but small studies show no adverse effects on COC absorption[23,24].

Eli Lilly has provided data showing that administration of a COC (0.035 mg ethinyl estradiol plus 0.25 mg norgestimate) in the presence of a single dose of tirzepatide (5 mg) resulted in a reduction of oral contraceptive Cmax (maximum drug concentration) by 55 to 66%, with a 16 to 23% reduction in AUC (Area Under the Curve) and a delay in Tmax (time to achieve Cmax) of 2.5 to 4.5 hours. These effects may be due to the impact of tirzepatide on gastric emptying. The company therefore advises patients using a COC to switch to a non-oral contraceptive method, or to add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation with tirzepatide[25].

Potential drug interaction between tirzepatide and oral progesterone

A review of drug-drug-interaction (DDI) based on the pharmacological profiles described in the SmPC provided by Eli Lilly resulted in possible interactions:

- From a pharmacokinetic perspective, tirzepatide might impact the absorption of progestogen (similar to COC[25]).
- The pharmacodynamic properties based on the mode of action do not reveal a particular risk of pharmacodynamic interaction. However, diabetes mellitus belongs to the conditions that may be aggravated during treatment with progestogens. An adjustment in anti-diabetic dosage may be required for women being treated concomitantly with progestogen[26].
- The safety profiles of tirzepatide and progestogen show some overlap in the system organ classes, "Gastrointestinal disorders" (including gall bladder related conditions), "Skin and subcutaneous tissue disorders" (such as alopecia/hair loss), and "Immune system disorders" (hypersensitivity). Whether a concomitant use increases the risk of adverse events is unknown. For a full description of the safety profile please see section 4.8 of the respective SmPC[25,26].

Progestogens and unscheduled vaginal bleeding on HRT

Unscheduled bleeding on HRT is well recognised and can affect up to 40% of users[27] and a recent increase in referrals to the urgent suspicion of cancer pathway for unscheduled bleeding in the UK has necessitated a formal national consensus guidance to support clinicians[28]. Women with an intact uterus using estrogen therapy above regulator approved doses should consider having their progestogen dose increased (irrespective of use of incretin-based therapies) to ensure adequate endometrial protection. Research data are lacking; therefore, dosing guidance is based on expert opinion.

The increased uptake of modern HRT formulations outside clinical trials may be linked to the unexpected rise in unscheduled bleeding in UK women using HRT in recent years. The characteristics of women accessing HRT in clinical practice may differ from those of clinical trial participants, with a higher occurrence of comorbidities such as obesity[21].

During the last 2 years, since semaglutide and tirzepatide received licenses for weight loss, there has been an increase in uptake of these medications through private clinics, while NHS prescribing is limited to specialist weight management services.

There are no current data available about numbers of women receiving HRT concurrently with semaglutide or tirzepatide. There are no data providing evidence of any impact of semaglutide or tirzepatide on the oral progestogen component of HRT, dosing requirements, bleeding patterns or endometrial risk. While there is a lack of evidence, incretin-based therapies would be unlikely to impact transdermal progestogen within combined patches or vaginal route-progestogen when used as part of HRT. However, vaginal route progesterone does not have a license for HRT use.

The 52 mg Levonorgestrel releasing intrauterine device provides contraception in perimenopausal women and endometrial protection for the estrogen component of HRT, unaffected by concomitant use of semaglutide or tirzepatide. This is therefore likely to be the most comprehensive option for endometrial protection in women using combined HRT concomitantly with semaglutide or tirzepatide for obesity/diabetes (expert opinion).

A pragmatic approach to adjusting progesterone dosing with different HRT preparations, based on limited available evidence, is summarised in box below:

Current progestogen	Recommendation
Combined patch	No change
LNG-IUD up to 5 years	No change
Oral progestogen/progesterone*	Consider changing to LNG-IUD/increase dose of progestogen/progesterone at initiation for 4 weeks and maintain higher dose for 4 weeks after any dose increment
Vaginal progesterone (off licence)	No change

* Weight loss injections may reduce the effectiveness of oral HRT medications. Review of current HRT is recommended while using these medications.

Summary point

Concerns related to concurrent use of HRT and semaglutide or tirzepatide relate primarily to endometrial protection and a potential risk of reduced absorption of oral progestogens used within HRT regimens.

General Guidance

1. In women with obesity there is an increased risk of endometrial hyperplasia, cancer and death from endometrial cancer.
2. Sustained weight loss in women with obesity appears to reduce endometrial risk.
3. In women with obesity/overweight with comorbidities and diabetes, the transdermal route for estrogen is preferred and this is also the case with concomitant use of incretin-based therapies.
4. Incretin-based therapies delay gastric emptying and therefore may reduce the absorption of any oral component of HRT.
   a. Extrapolating from data on COC effects indicates that using non-oral progestogen for 4 weeks after initiation and for 4 weeks after each dose escalation with incretin-based therapies may be needed for effective endometrial protection.
   b. From a pragmatic perspective, with several potential dose changes, a non-oral route for the progestogen component of HRT would be preferable throughout treatment with incretin-based therapies.
   c. The 52 mg Levonorgestrel releasing intrauterine device provides contraception in perimenopausal women, and endometrial protection for the estrogen component of HRT, unaffected by concomitant use of incretin-based therapies. This is therefore likely to be the most comprehensive option for endometrial protection in women using combined HRT concomitantly with incretin-based therapies for obesity/diabetes (expert opinion), particularly since this group of women are already at increased risk of endometrial pathology.
5. Where oral progestogen is preferred by patients on HRT, there are no data to inform the dose adjustment required for endometrial protection in high-risk women, including those treated with incretin-based therapies.
   a. A potential approach is to temporarily increase the dose of oral progestogen for 4 weeks after commencing incretin-based therapies, and maintain a higher dose of progestogen with each dose increment on incretin-based therapy until a stable dose is achieved. This is based on extrapolation from COC data and intuitive expert opinion. Uncertainty should be shared with the patient to aid informed decision making.
   b. In the presence of unscheduled bleeding in women using HRT and incretin-based therapies, national consensus guidance should be followed[28].
6. Women who continue to have unscheduled bleeding despite modifying their progestogen intake while using incretin-based therapies, or where there is a concern about the clinical presentation, bleeding amount, or pattern, should be assessed to exclude endometrial pathology. It may be prudent to consider investigations earlier than stated in national guidance in high-risk women (expert opinion).

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PUBLICATION DATE: APRIL 2025
REVIEW DATE: APRIL 2028

Q3P2425

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Reg Charity No: 1015144
Company Reg No: 02759439