Supplementary Information

Summer –June 2026

GLP-1 Receptor Agonists

Glucagon-like Peptide Receptor Agonist (GLP-1 RA), including **semaglutide, tirzepatide and liraglutide** are licensed for obesity/weight management and management of Type 2 diabetes mellitus (T2DM). The use of GLP-1 RA has increased markedly over the past decade, particularly among women of reproductive age. While this is primarily driven by use for licensed indications, these agents may also be used off-license in the treatment of infertility related to polyendocrine metabolic ovarian syndrome (PMOS) and female obesity-related hypogonadism.[1] GLP-1 RA associated weight loss has been proposed as a way to improve fertility among women with obesity, however formal evidence to support this is not available.

The Market Authorisation Holders for GLP-1 RAs recommend that these agents should not be used during pregnancy or in women of childbearing potential who are not using effective contraception, and should be discontinued if a patient wishes to become pregnant or if pregnancy occurs. The Health Products Regulatory Authority (HPRA) echoed this in a recent drug safety newsletter.[4]

With regards to preconception planning, **the recommended interval between discontinuing GLP-1 RA and trying to conceive varies by agent,** reflecting differences in drug half-life and pharmacokinetics[2] (e.g. 2 months for semaglutide and 1 month for tirzepatide). Similar recommendation are contained in expert guidelines on the management of pre-existing diabetes from the Endocrine Society and European Society of Endocrinology recommend.[1–3] It is important to note that The Faculty of Sexual and Reproductive Healthcare (FSRH) have also published recommendations on the use of oral contraceptives with GLP-1 agonists.

GLP-1 RA and early pregnancy exposures

Despite regulatory recommendations regarding discontinuation of GLP-1 RA prior to conception, reports of inadvertent exposures to GLP-1 RA in early pregnancy are increasing. While GLP-1 RAs may offer several potential benefits for cardiometabolic health, important safety concerns regarding their use in pregnancy must be considered, in addition to potential nutritional and metabolic complications such as inadequate caloric intake and dietary deficiencies.

Preclinical animal studies with GLP-1 RA reported evidence of adverse fetal effects including reduced fetal growth and increased abnormalities of fetal vessels and skeleton. These studies involved exposures above the human therapeutic exposure, but in some cases doses were below the recommended human dose. There was decreased maternal weight gain and food consumption in line with the pharmacological effects of GLP-1 RA.

Published data on human pregnancy outcomes following inadvertent GLP-1 RA exposure in early pregnancy are increasing. **Accumulating evidence offers reassurance to women with inadvertent exposure in early pregnancy**. Available evidence was summarised in a recent systematic review that

included thirty-six studies reporting GLP-1 RA use during preconception, pregnancy, and during lactation. Studies included case reports, case series, retrospective and prospective cohort studies. Conclusions were such that pre-conceptional or early-pregnancy exposure to **GLP-1-based therapies is not consistently associated with increased maternal, fetal, or neonatal risk**, compared with insulin-treated or disease-matched controls, although data on continued use throughout gestation remain limited.[5]

Although still somewhat limited, available data provide reassuring evidence that **GLP-1 RA are not associated with major congenital malformations (MCM).** For example, one observational population-based cohort study from across 6 countries included 938 women with pre-gestational T2DM who had periconceptional exposure to GLP-1 receptor agonists (n=461 in 1st trimester). While the study did find an elevated rate of major congenital malformations (MCMs) among women with T2DM (5.3%) compared to the general population rate (3.7%), this is in line with previous studies for women of a similar cohort. When compared with insulin, the authors did not observe an elevated risk of MCM after periconceptional or first trimester exposure to GLP-1 RA, suggesting GLP-1 RAs did not increase the risk of MCMs above the risk conferred by maternal T2DM.[6]

Similarly, findings from a study involving six Teratology Information Services, offers **reassurance in cases of inadvertent exposure to GLP1-RA during the first trimester of pregnancy**. This multicentre, observational, prospective cohort study compared pregnancy outcomes in women exposed to GLP1-RA in early pregnancy either for diabetes or obesity treatment (n=168) to women with diabetes exposed to at least one non-GLP1-RA antidiabetic drug during the first trimester (n=156) and a reference group of overweight/obese women without diabetes (n=163). They found exposure to GLP-1-RA in the first trimester was not associated with a risk of major birth defects when compared with diabetes (2.6% vs 2.3%; adjusted OR, 0.98 (95% CI, 0.16 to 5.82)) or to overweight/obese (2.6% vs 3.9%; adjusted OR 0.54 (0.11 to 2.75)).[7] **Rates of spontaneous abortion were within expected background ranges.** Other studies have used EHR data have reported conflicting results.[8]

GLP-1 RA and other pregnancy outcomes

Data are also evolving on other pregnancy outcomes following GLP-1 RA exposure. A recent observational cohort study using data from the Danish health registries provides **reassurance regarding the risk of other obstetric outcomes, and preterm delivery in particular**. [10] In this large study, which included 529 GLP-1 RA exposed pregnancies, the authors initially found higher rates of multiple obstetric complications among exposed women, but these were not found to be significant in adjusted analyses. The authors also reported periconceptional GLP-1 RA use was associated with increased risk of preterm birth when used for diabetes treatment (liraglutide aOR 1.70, 95% CI 1.17–2.48; semaglutide aOR 1.84, 95% CI 1.24–2.7) but not for weight management (liraglutide aOR 1.01, 95% CI 0.58–1.76; semaglutide aOR 0.71, 95% CI 0.30–1.70). This suggests **underlying diabetes may be the causal factor in the observed increase in preterm delivery, rather than the medication exposure**.[9] Likewise, Bartelt et al. reported similar rates of preterm birth among GLP-1 RA exposed (n=1208) and non-exposed (n=771,087) when adjusted for maternal age and BMI using a US-based electronic health record (EHR).[10]

Some studies using retrospective EHR data from the United States (US) have also reported **lower risk of cardiometabolic complications in those prescribed GLP-1 RA**. For example, Hanif et al. reported no increased risk of gestational hypertension, preeclampsia or maternal mortality among 1826 women exposed to GLP-1 RA before or during the first trimester of pregnancy compared to non-exposed pregnancies.[11] Similarly, Pondugula et al. reported lower odds of hypertensive disease in pregnancy among 243 women who had periconception and first trimester exposure to GLP-1 RA compared with those on other or no anti-diabetic medication.[12] Lower risks of GDM, hypertensive disease in pregnancy, preterm delivery and caesarean section were also reported among women exposed to GLP-1 RA within 24 months before pregnancy when compared with matched unexposed pregnancies. Similar findings were reported when limited to women exposed within the 12, 6 and 3 months before pregnancy.[13]

However, some conflicting are available; another observational cohort study, also using retrospective EHR data from 448 GLP-1 RA exposed pregnancies in the US, reported increased maternal complications including GDM, hypertensive disorders and preterm birth in those who discontinued GLP-1 RA therapy before or in early pregnancy (n=448) compared with unexposed pregnancies (n=1344).[13]

A review published earlier in 2026 focused on maternal cardiometabolic health and identified a number of **key knowledge gaps around the role of GLP-1 receptor agonists from preconception to postpartum** (Figure 1).[1]

Key knowledge gaps and their implications in GLP-1 agonist use across the reproductive periods.

Domain	Gap Identified	Implication for Practice
Preconception / Safety	Limited human data on fetal effects: growth restriction, embryonic/fetal death, or APO risk.	Clinicians must counsel on uncertain fetal risks.
Preconception / Tolerability	Gastrointestinal side effects and potential lean muscle loss may limit adherence or affect metabolic readiness for pregnancy.	Need for monitoring, dietary support, and potential discontinuation based on tolerability.
Preconception / Timing of Discontinuation	Optimal duration of discontinuation and potential benefits of continued therapy are unknown; conflicting observational data on gestational weight gain and APOs.	Therapy held prior to conception. Unclear whether continued or modified use could confer maternal metabolic or fetal benefit; clinicians must counsel on uncertainty.
Postpartum / Safety, Efficacy, and Timing	Lack of evidence on safety, efficacy, and timing for initiation or resumption postpartum.	Clinicians should consider metabolic/CVD benefits with breastfeeding and future family planning.
Postpartum / Long-Term CVD Prevention	Role in reducing postpartum cardiometabolic risk and maintaining weight/ metabolic benefits is not studied.	Missed opportunity to optimize long-term cardiovascular outcomes in high-risk populations; need for adjunctive or complementary strategies.

Abbreviations: APO, adverse pregnancy outcome; CVD, cardiovascular disease; GLP-1, glucagon-like peptide-1; OB/GYN, obstetrics and gynecology.

Figure 1: Key Knowledge gaps and their implications in GLP-1 agonist use across reproductive periods.[1]

Discontinuation of GLP-1 RA

Similar to non-pregnant populations, rapid weight regain and worsening cardiometabolic health have been suggested following discontinuation of GLP-1 RA before or in early pregnancy.[14] Although limited, **some studies have reported greater gestational weight gain (and increased maternal complications) following GLP-1 RA discontinuation** compared with unexposed women[14]. Others have reported similar effects on weight gain for women using GLP-1 RA for weight management and not for pre-gestational diabetes.[12]

Risks and benefits may vary by timing of exposure, metabolic profile, and reproductive stage. The Endocrine Society consider the timing of discontinuation prior to pregnancy particularly important for individuals' with T2DM. They recommend **an individualised approach with timely transition and titration of alternative anti-hyperglycemic agents after discontinuing GLP-1 RAs** in order to minimise hyperglycaemia and weight gain associated with sudden discontinuation.[3] Additional research is therefore necessary to inform recommendations around the use of these agents in women of child bearing potential and the timing and schedule of discontinuation. Furthermore, decisions to initiate or resume GLP-1 RA therapy in the postpartum period needs individualisation, taking metabolic indication, breastfeeding status, contraceptive use, family planning, and alternative or complementary approaches into consideration.[1]

Opioid Use Disorder

Opioid use disorder (OUD) during pregnancy can pose significant harm to maternal and fetal health including overdose, pre-term birth, neonatal complication and maternal and fetal death.

Methadone has been the standard treatment for OUD in pregnancy for more than three decades supported by a **substantial body of observational evidence for improved maternal, pregnancy and infant outcomes compared with untreated OUD or withdrawal approaches**. While methadone remains essential for individuals with higher opioid dependence or more complex clinical and social needs,[15] the use of buprenorphine as an alternative treatment is increasingly used in many settings.[15] Emerging evidence suggests **buprenorphine is associated with improved birth outcomes and reduced severity of neonatal abstinence syndrome** compared with methadone. How it compares to methadone for neurodevelopment and long-term child outcomes is not fully established.

OUD and Neurodevelopmental outcomes – PRAC routine periodic safety assessment

As part of a routine periodic safety assessment, the European Medicines Agency Pharmacovigilance Risk Assessment Committee (EMA PRAC) reviewed evidence of neurodevelopmental impairment in children born to opioid-dependent mothers. This included several studies that reported an apparent association between methadone and neurodevelopmental disorders.[17–21] In most studies, the association was no longer present or was attenuated once adjusted for confounding factors. In others, confounding by indication and residual confounding related to genetics, environmental risk factors and socioeconomic status were considered possible. Study limitations included small sample sizes, unexposed comparator groups, inconsistent/inadequate adjustment for confounding factors, and inconsistent measurement tools used for 'neurodevelopmental' outcomes. **The PRAC concluded there is insufficient robust evidence to suggest a causal relationship between prenatal exposure to methadone and neurodevelopmental impairment in children.**

This is supported by a large and methodologically robust US population based cohort study recently published in the British Medical Journal.[22] This study compared the risk of neurodevelopmental disorders in the first eight years of life among children prenatally exposed to methadone vs buprenorphine. The study adjusted for age, race, severity of opioid-use-disorder, co-occurring substance use diagnosis, co-morbidities, concomitant medication and prenatal care differences and also conducted trimester specific analysis. **Results did not find an overall increase in specific neurodevelopmental disorders for buprenorphine compared to methadone.** Furthermore, trimester specific analysis provided reassurance that exposure later in pregnancy, when cognition, memory and behaviour develop rapidly was not associated with increased neurodevelopmental risk.[22]

Long-acting buprenorphine

Longer acting injectable buprenorphine is becoming increasingly popular in high-income countries due to its potential advantage over sublingual buprenorphine regarding the risk of diversion, adherence and daily peak-trough effects.[15,23] Findings from the first randomised control trial

comparing extended release to sublingual buprenorphine during pregnancy through 12 months postpartum, **support weekly extended-release buprenorphine for OUD treatment during pregnancy**. The study, conducted at 13 US sites between July 2020 and October 2024, included 140 randomized participants and had a completion rate of 98% through pregnancy (137 participants) and 81% through 12 months post-partum (114 participants). Illicit opioid abstinence was higher during pregnancy for participants receiving extended-release vs sublingual buprenorphine (82.5% vs 72.6%; mean difference, 9.84 [95% CI, 1.72 to 17.95] percentage points; P = .009). Postpartum abstinence rates declined and were similar in both groups (60.2% vs 59.5%; mean difference, 0.65 [98% CI, −12.72 to 14.02] percentage points; P = 0.45). Infants exposed to extended-release vs sublingual buprenorphine did not differ in need for opioid treatment (30.2% vs 26.5%; relative risk, 1.14 [98% CI, 0.54 to 1.99]; P = 0.64) or mean (SE) treatment days (10.9 [2.2] vs 14.8 [3.0] days; relative risk, 0.73 [98% CI, 0.36 to 1.51]; P = 0.28). Other maternal and infant outcomes were generally similar between the two groups.[23]

While once monthly injections have been shown to reduce the risk of misuse, diversion and support recovery goals, there have been some concerns about the reproductive and developmental safety of excipients in monthly formulations such as N-methyl-2-pyrollidone (NMP). Recent animal research does not suggest NMP has adverse fetal-infant effects and the US Food and Drug Administration Agency (FDA) labelling was updated to remove the previously stated potential effect. Long acting buprenorphine injections are not contraindicated in any of the approved markets globally such as the US, Canada and Europe including Buvidal® licensed in Ireland.[24] The summary of products characteristics (SPC) does state however ''Buprenorphine should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus''.

Sapropterin (Kuvan®) in Pregnancy – PRAC update May 2026

Phenylketonuria (PKU) is an autosomal recessive condition, occurring in approximately 1 in 4000 new-borns in Ireland.[25] It is characterised a deficiency in the enzyme phenylalanine hydroxylase which prevents metabolism of the amino acid phenylalanine (Phe) and subsequently increases its concentration.

Phe crosses the placenta via active transport resulting in 70-80% increased concentrations in the new-born compared to maternal concentrations. **Uncontrolled maternal Phe levels during pregnancy are known to be harmful to the mother and the fetus**.[26,27] In untreated pregnancies wherein the mother has classic PKU with a blood Phe level greater than or equal to 1,200 microM (20 mg/dl), the frequencies of these abnormalities in offspring are exceedingly high, approaching 75-90% for microcephaly and neurodevelopmental impairment, and 15% for congenital heart disease.[26]

It is essential that Phe levels are well controlled prior to and during pregnancy given the teratogenic effects associated with high Phe levels and consequential maternal PKU syndrome. A clear dose response effect has been observed for these teratogenic effects (Figure 2 and 3).[26,28] Restriction of dietary Phe intake is the cornerstone of managing serum levels prior to and throughout pregnancy. Sapropterin (Kuvan®) is a drug licensed to reduce Phe serum levels and treat hyperphenylalaninaemia (HPA) and PKU in those who have been shown to be responsive to such treatment.[29]

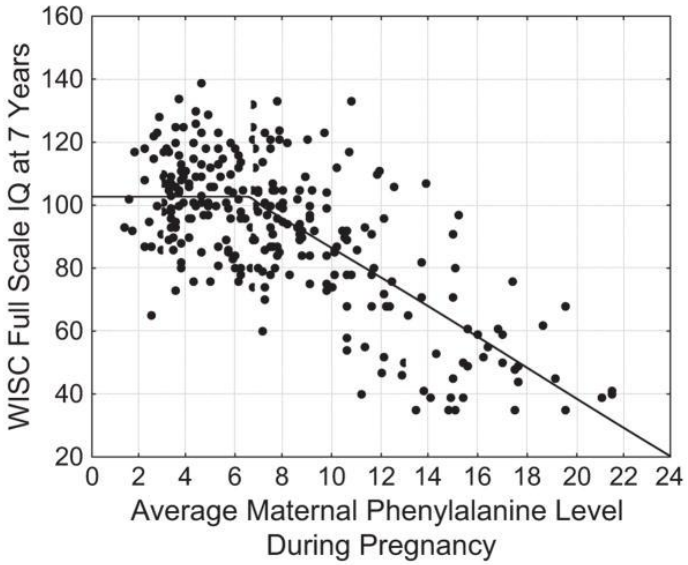

Figure 2: Relation of average phenylalanine in maternal blood during pregnancy and child Wechsler Intelligence Scale for Children (WISC)-Revised IQ scores at age 7 years.[28]

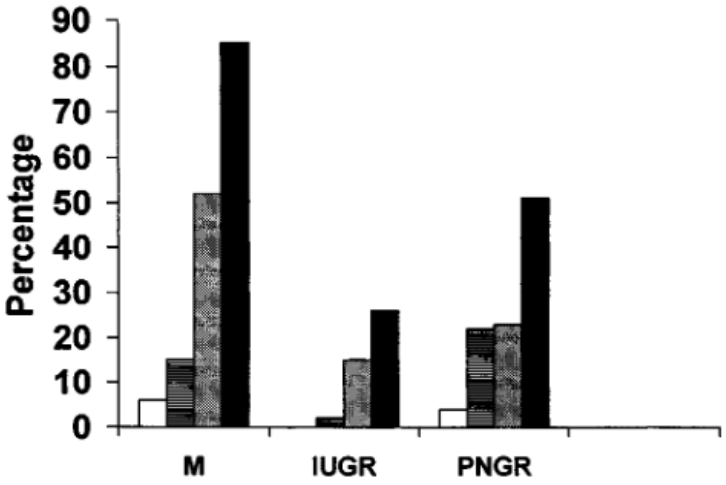

Fig. 3. Relationship between brain, fetal, and body growth and blood Phe (μmol/liter) during gestational weeks 8–12. M, microcephaly; IUGR, intrauterine growth retardation; PNGR, postnatal growth retardation. $P < 0.005$. □ 120–360 (n = 48); ▤ 361–600 (n = 41); ▩ 601–900 (n = 52); ■ > 900 (n = 47).

Figure 3: Relationship between neurological abnormalities and average Phe exposure (μmol/liter).[25]

During their meeting in May 2025, the Pharmacovigilance Risk Assessment Committee (PRAC) considered the available data on sapropterin in pregnancy. This included published data on from the

US-based sub-registry study 'PKU-MOMS', the 'KAMPER' registry in the EU and a report from the pharmaceutical company that markets Kuvan® of cumulative exposure data relating to sapropterin use during pregnancy and breastfeeding. The PRAC noted that due to data limitations, including small sample sizes, incomplete information on exposure timing and maternal Phe control, and confounding by underlying disease, **no conclusions could be drawn on the risk of specific pregnancy/neonatal outcomes associated with sapropterin exposure in utero.**

An update to section 4.6 of the SPC was recommended to reflect current pregnancy exposure data, to emphasise the risks associated with uncontrolled maternal Phe levels and the importance of maintaining strict control before and during pregnancy.[30] Despite the limited data, **sapropterin may be considered for use during pregnancy in selected patients where indicated**, particularly where adequate phenylalanine control cannot be achieved with dietary management alone.

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