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REVIEW

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What is known about the use of weight loss medication in women with overweight/obesity on fertility and reproductive health outcomes? A scoping review

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Summary

Pregnancy during or soon after treatment with weight loss medication, particularly glucagon-like peptide-1 receptor agonists (GLP-1 RAs), is contraindicated due to potential teratogenicity. The aim of this scoping review is to investigate what is known about the use of weight loss medication in women of childbearing age in relation to reproductive health outcomes, focusing on the three medications licenced in the United Kingdom at the time of the search. A systematic search of studies that assessed reproductive health outcomes in women taking either orlistat, liraglutide or semaglutide was undertaken in July 2023 and updated in January 2024 across MEDLINE, Embase, CINAHL, Scopus, ClinicalTrials.gov, PROSPERO, Epistemonikos and OpenGrey. Studies focused on polycystic ovarian syndrome, diabetes or animals were excluded. Titles and abstracts were screened, and data from included articles were extracted. After removal of duplicates, 341 titles remained, of which 318 were excluded. Of the final 18 articles included, there were five interventional trials, one retrospective case-control study, six narrative reviews, two systematic reviews, three systematic review protocols and one registry protocol yet to start recruitment. All five interventional trials involved orlistat given preconceptionally, showing no improvement in live birth rate, despite improvement in reproductive hormone levels. There were no studies with primary data about GLP-1 RAs. There were no qualitative studies. There is an absence of primary data about the role of GLP-1 RAs on the reproductive health of women of childbearing age without polycystic ovarian syndrome. Future research should explore short- and long-term effects on reproductive health, pregnancy outcomes and experiences.

KEYWORDS

GLP-1 receptor agonists, infertility, liraglutide, pregnancy, semaglutide

Registration: The review protocol is registered on Open Science Framework: https://osf.io/b72ge/?view_only=b2446ba544ec4d78ad2eebcb14dac4c4.

What is already known about this subject

- Obesity in reproductive-age women is very common.
- Weight loss medications are contraindicated during pregnancy, but little is known about how they are used preconceptionally and the implications for fertility and subsequent pregnancy.

What this study adds

- There are no primary data about the use of glucagon-like 1 peptide receptor agonists and reproductive outcomes in women who do not have polycystic ovarian syndrome or diabetes.
- Similarly, there is no qualitative research on this topic.
- Further research is needed on the safety of weight loss medications before pregnancy and the experiences of women using them for fertility reasons. Practitioners should clearly communicate the risk of teratogenic effects and the need for concurrent contraception.

1 | INTRODUCTION

Obesity in people of childbearing age is a global concern with pre-pregnancy overweight/obesity affecting 42%, 30% and 10% of women in the United States, Europe and Asia, respectively.[1] Obesity is associated with fertility and reproductive complications with evidence that weight loss improves the likelihood of a successful pregnancy.[2] In the United Kingdom (UK), less than 50% of women start pregnancy with a body mass index (BMI) in the healthy range,[3] as such there is an increasing emphasis on optimisation of weight toward the healthy range *before* pregnancy.[4]

Due to the high prevalence of obesity combined with limited access to publicly funded weight management services, including bariatric surgery,[5] there is an urgent need for well-tolerated and effective pharmacologic weight loss therapy.[6] At the time of writing, there are currently only three licenced weight loss medications in the UK: orlistat, liraglutide and semaglutide. Orlistat, which partially inhibits hydrolysis of triglycerides and subsequent absorption,[7] is prescribed with a lower dose and is available over the counter. Liraglutide and semaglutide are both glucagon-like peptide-1 reception agonists (GLP-1 RAs), which work by increasing insulin secretion, suppressing glucagon secretion, slowing gastric emptying, and suppressing appetite.[8,9] They are both formulated as a self-injected pen, available on prescription according to specific eligibility criteria, namely in specialist weight management clinics as an adjunct to a reduced-calorie diet and increased physical activity for weight management.[10] Both can also be prescribed through a private healthcare provider online and can be purchased online from unregulated websites.

Pregnancy during or soon after treatment with weight loss medication is contraindicated due to potential for teratogenicity.[7–9,11] Animal studies of GLP-1 RAs have shown reproductive toxicity and the potential risk for humans is unknown.[12] Data on the safe and effective use of contraception with concomitant use of weight-loss medication are extremely limited and advice should be provided that medications that induce gastrointestinal side effects could reduce the effectiveness of oral contraceptives.[7,13] In those with excess weight-induced anovulation, weight loss may cause ovulation to recommence; hence, contraception should be recommended during any overlap between treatment and possible pregnancy,[14] with a 2-month gap between treatment and planned conception recommended for semaglutide.[8]

Several systematic reviews have investigated the role of weight loss medication in those with polycystic ovarian syndrome (PCOS)[15,16] reporting improvements in menstrual regularity and natural pregnancy rate with use of GLP-1 RAs. There are some isolated case reports about exposure to GLP-1 RAs in pregnancy in those with diabetes or PCOS.[17–19] However, to our knowledge no scoping review has been undertaken regarding licenced weight loss medication and reproductive health of women of childbearing age with overweight/obesity more generally. Scoping reviews are particularly useful in synthesising literature in emerging fields to map the extent, range and nature of the available literature.[20] The aim of this scoping review therefore is to investigate what is known about the use of weight loss medication in those of childbearing age in relation to fertility and reproductive health outcomes, with a specific focus on the three licenced medications available in the UK at the time of writing.

2 | METHODS

2.1 | Study design

This review used scoping methods, following the search strategy of the Joanna Briggs Institute[21] and the principles of Arskey and O'Malley's framework.[22] The key phases of this approach are identifying the research question, identifying relevant studies, study selection, charting the data and collating summarising and reporting the results.

2.2 | Identifying the research question

The scoping review addresses the following question: 'What is known about the use of weight loss medication in women with overweight/obesity on fertility and reproductive health outcomes?'

2.3 | Search strategy

A systematic search of studies that assessed fertility and reproductive health outcomes in women taking either orlistat, liraglutide or semaglutide was carried out. The search strategy was designed to find both published and unpublished articles in any language from 2000 to July 2023. The year 2000 represents the start of the period publications appeared in the literature after orlistat was licenced in the UK. The search was updated on 3rd January 2024 prior to submission of the manuscript.

A keyword search strategy based on Population, Intervention and Outcome, combining terms associated with obesity, weight loss medication and fertility/reproductive health was created through an iterative process. Key words are shown in Table S1.

Inclusion and exclusion criteria are shown in Table S2. Studies of participants with PCOS and/or diabetes were excluded. No limits were placed on parity, whether weight loss medication was monotherapy or combined therapy, duration of intervention, language, or study design. Studies that were focused solely on weight loss or body composition outcomes (i.e. did not include any outcomes related to fertility or reproductive health) were excluded, as were studies about animals or men. As this was a scoping review, a broad approach was taken, meaning articles not including original data such as protocols, editorials, narrative reviews, and opinion papers were eligible to be included.

A three-step search strategy was used, following the Joanna Briggs Institute approach.[21] The first step was an initial limited search of MEDLINE and CINAHL. This initial search was followed by an analysis of the text words contained in the title and abstract of retrieved papers and of the index terms used to describe the articles. A second search using all identified keywords and index terms was then undertaken across the following databases: MEDLINE (via Ovid), Embase (via OVID), CINAHL (via EBSCOhost) and Scopus. Additional searches were performed in ClinicalTrials.gov, PROSPERO and Epistemonikos databases. Grey literature was searched via Open Grey.

2.4 | Screening

Two independent reviewers (RA and KM) screened the titles and abstracts of all papers identified to determine if they met the inclusion criteria, using Raayan software.[23] Any disagreements were resolved through discussion with a third reviewer (JS).

Of the screened articles, full texts were retrieved, and these were assessed again by the same two independent reviewers. The reference lists of the included articles were hand-searched to detect any additional studies.

2.5 | Charting and summarising the data

Data were extracted from the full-text papers by two independent reviewers (KM and JS), using a predefined data collection proforma. The data collection form contained information on study characteristics (e.g. author, year of publication), design and methods (e.g. population characteristics, inclusion, and exclusion criteria), exposure, outcome measures, results and conclusions/recommendations.

For quantitative data, descriptive analyses in the form of percentages and frequency counts of concepts, populations, or locations, and other data categories were presented within tables/charts, accompanied by narrative summaries. As this was a scoping review, quality assessment of retrieved articles was not conducted.

The conduct and findings of the scoping review were reported in accordance with the PRISMA Extension for Scoping Reviews[24] (see Supplementary file).

3 | RESULTS

3.1 | Literature search results

Search results are shown in the PRISMA flowchart (Figure 1). The initial search yielded 452 articles. After removal of duplicates, 341 titles remained, of which 318 were excluded on title and abstract screening. Twenty-two full-text articles were retrieved. For one study,[25] only the abstract was available. The abstract met the inclusion criteria and was included, as were 17 of the full-text articles, leaving 18 included articles overall. An overview of the included studies is shown in Table 1.

3.2 | Study characteristics

Of the final 18 articles, there were five interventional trials, one retrospective case-control study, six narrative reviews, two systematic reviews, three systematic review protocols and one registry study protocol (yet to start recruitment).

All five trial studies[25–29] were based on orlistat, as was the retrospective case-control study.[30] There were no studies with primary data about liraglutide or semaglutide that met the inclusion criteria of this scoping review. There were no qualitative studies.

3.3 | Orlistat

In total, there were six studies that investigated administration of orlistat preconceptionally, five intervention studies[25–29] and one retrospective case-control study.[30] Details are shown in Table 2. The studies were based across a wide geographical region: China, Russia, Egypt, Bangladesh and USA, with four of the studies published in the last 2 years. The intervention duration varied from 4 weeks to 6 months. All studies included women with a BMI >25 kg/m^2, however for Legro et al.[28] the BMI eligibility criteria was >30 kg/m^2.The studies varied widely in sample size, complexity and design, for example the study by Totoian et al.,[25] had the smallest sample size ($n = 17$) with no control group, whereas the study by Wang et al.[27] had 877 participants, 439 of who were given orlistat, as part of a

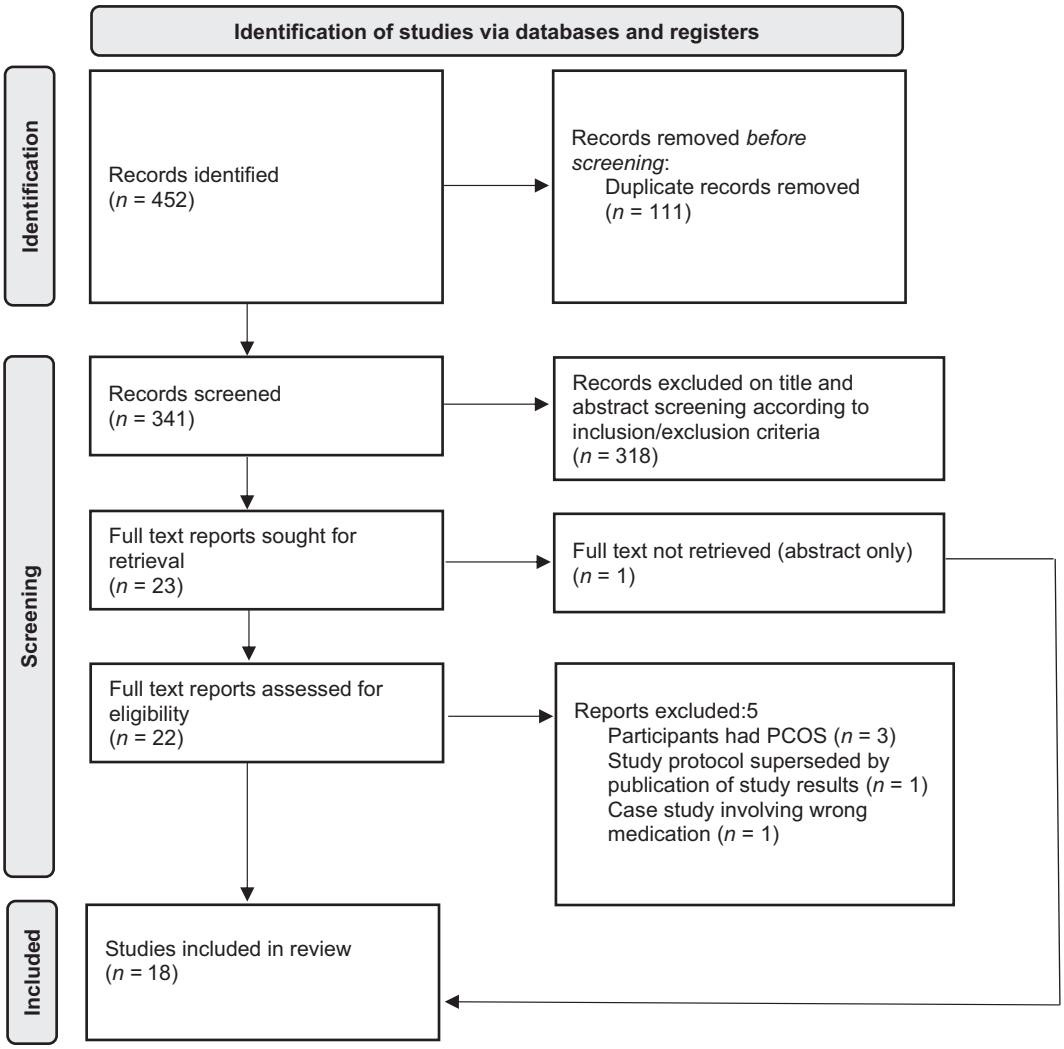

FIGURE 1 PRISMA flowchart.

randomised double-blind placebo multisite trial. There was also heterogeneity in the comparator groups across studies. For example, in Legro et al.[28] the control group had a digitally monitored physical activity target of 10 000 steps/day, whereas for Al-Qahwajy et al.,[29] advice was provided about caloric reduction and increased physical activity.

Three of the studies administered orlistat prior to participants undergoing fertility treatment.[27,28,30] None of these studies reported a significant difference in the live birth rate comparing the orlistat and control groups, despite significantly higher weight reduction and improvement in reproductive and metabolic parameters in the orlistat groups. One of these three studies reported a non-significant trend of increased first-trimester pregnancy loss in the orlistat group.[28] Fertility treatment was not included in the study design of the other three orlistat studies.[25,26,29] They demonstrated significantly greater weight reduction and improvement in some reproductive endocrine parameters but did not report on live birth rates due to the short follow-up timeframe of the studies.

3.4 | GLP-1 RAs: Liraglutide and semaglutide

There were no completed primary studies about either liraglutide or semaglutide. There were six narrative reviews,[14,31–35] two systematic reviews about weight loss medications[12,36] and one protocol for a planned pregnancy registry study.[37]

3.5 | Narrative reviews

None of the six narrative reviews included any new studies that met the inclusion criteria of the scoping review. One of the narrative reviews was concerned with women with endometrial cancer and the potential for GLP-1 RAs to be used as an adjunct in fertility-sparing treatment.[33] The other five articles[14,31,32,34,35] were about the use of GLP-1 RAs in women of reproductive age more generally. Although there were nuances in how authors approach and discuss the topic, all emphasised the potential for teratogenic effects, the importance of

TABLE 1 Overview of included studies and sources of funding.

First author	Publication year	Title	Design	Funding
Al-Qahwajy	2022	Orlistat (the Lipase Inhibitor) therapy in overweight and obese subfertile women	Trial	Not stated
Legro	2022	Effects of preconception lifestyle intervention in infertile women with obesity: the FIT-PLESE randomised controlled trial	Trial	US National Institutes of Health, National Center for Advancing Translational Sciences, Nutrisystem, Fitbit
Rahman	2017	Orlistat (the Lipase Inhibitor) therapy in overweight and obese subfertile women	Trial	Not stated
Wang	2021	Effect of orlistat on live birth rate in overweight or obese women undergoing IVF-ET: a randomised clinical trial	Trial	National Key Research and Development Program of China, Taishan Scholar Project Special Funds of China and the Shandong Provincial Key Research and Development Program of China
Totoian[a]	2006	[Use of orlistat (xenical) in the treatment of women with obesity and disorders of menstrual cycle]	Trial	Information not available
Tong	2022	Effect of orlistat intervention on in vitro fertilisation/intracytoplasmic sperm injection outcome in overweight/obese infertile women	Retrospective case-control study	No external funding
Gill	2021	Obstetrician-Gynaecologists' strategies for patient initiation and maintenance of antiobesity treatment with glucagon-like peptide-1 receptor agonists	Narrative review	Writing and editing support were funded by Novo Nordisk, Inc.
Goldberg	2023	Navigating the role of anti-obesity agents prior to pregnancy: a narrative review	Narrative review	Not stated
Jensterle	2019	The role of glucagon-like peptide-1 in reproduction: from physiology to therapeutic perspective.	Narrative review	No external funding
Minis	2023	Glucagon-like peptide-1 receptor agonists and safety in the preconception period	Narrative review	National Institute of Diabetes, Digestive and Kidney Diseases of National Institutes of Health
Nuako	2023	Pharmacologic treatment of obesity in reproductive-aged women	Narrative review	No funding stated
Violette	2023	The potential role of GLP-1 receptor agonist targeting in fertility-sparing treatment in obese patients with endometrial malignant pathology: a call for research	Narrative review	This paper received an Ensign Endowment for Gynecologic Cancer Research
Taghavi	2021	Pharmacological and non-pharmacological strategies for obese women with subfertility	Systematic review	Cochrane
Muller	2023	Effects of GLP-1 agonists and SGLT2 inhibitors during pregnancy and lactation on offspring outcomes: a systematic review of the evidence	Systematic review	No external funding
Ruiz-Gonzalez	2022	Effects of pharmacological and/or weight loss strategies on hormonal profile in women at fertile age with overweight or obesity. A systematic review and network meta-analysis.	Systematic review protocol	None
Ma	2022	Effect of preconception intervention on pregnancy outcome in obese/overweight women undergoing IVF/ICSI – a systematic review and meta-analysis	Systematic review protocol	None
Guo	2023	Efficacy of weight-loss interventions for improving fertility in overweight or obese infertile women: a systematic review and meta-analysis	Systematic review protocol	None
Novo Nordisk	2023	a study to evaluate safety of exposure to wegovy during pregnancy	New registry study	Novo Nordisk

[a]Abstract only.

TABLE 2 Details of trials and retrospective case-control study.

Citation (first author, year and country)	Study design	Population and sample size (including eligibility, age, BMI and co-morbidities)	Drug type and dosage	Control group	Duration of intervention	Main outcomes	Conclusion
Al-Qahwajy, 2022, Egypt	Randomised trial	$N = 120$ (60 in each group) Women aged 21–35 years with BMI between 25 and 40 kg/m^2 and primary infertility Orlistat group at baseline[a]: Mean age (SD): 28.57 (4.57) Mean BMI (SD): 30.91 (3.26)	120 mg orlistat twice daily	Lifestyle modification: reduced energy intake, increased physical activity	6 months	Significant decrease in LH, LH/FSH ratio, AMH in orlistat group. Increase in midluteal progesterone and ovulate size in orlistat group. Significantly more pregnancies in orlistat group compared to control group (14 vs. 4)	Reproductive endocrine parameters improved and higher rate of pregnancy in orlistat group
Legro, 2022, USA	Open-label randomised, multi-centre, controlled trial	$N = 379$ Women aged 18–40 years with BMI >30 kg/m^2 and unexplained infertility Orlistat group at baseline[a]: Mean age (SD): 32.1 (4.5) Mean BMI (SD): 39.2 (7.0)	Orlistat 60 mg per meal twice daily, alongside meal replacement plan of ∼1200 kcal/day and increased physical activity, with a 7% weight loss target. Physical activity goal of 10 000 steps per day set, monitoring digitally	Physical activity only (goal of 10 000 steps per day set, monitoring digitally)	16 weeks, followed by up to 3 cycles of standardised fertility treatment	No significant difference in healthy live births (15.2% control vs. 12.2% orlistat group). Orlistat group had a higher, but insignificant rate of first-trimester pregnancy loss (33.3% vs. 23.7% in control group). Orlistat group had significantly greater weight loss and decrease in metabolic syndrome compared to control group (−6.6 ± 5.4% vs. −0.3 ± 3.2% weight reduction and 20.6% vs. 4.2% reduction in metabolic syndrome)	The intervention did not improve fertility or birth outcomes compared to an exercise intervention without targeted weight loss. Improvement in metabolic health may not translate into improved female fecundity
Rahman, 2017, Bangladesh	Experimental randomisation not stated	Subfertile women with BMI 25–40 kg/m^2 aged 18–35 years with no history of taking medication or dietary modification for weight loss currently or for the preceding 3 months Orlistat group at baseline[a]: Mean age (SD): 27.31 (4.58) Mean weight (SD): 72.26 (7.81)	120 mg orlistat twice daily	Lifestyle modification: low glycaemic index diet and moderate exercise	3 months	Reduction of weight significantly higher in orlistat group in those with BMI of 25–29.9 kg/m^2 (6.52% vs. 5.33%). Ovulation assessed by transvaginal scanning improved more in orlistat group at 3 months (61.7% vs. 45.0%, but difference was not significant	Orlistat can improve ovulation more than lifestyle modification alone
Tong, 2022, China	Retrospective case-control study with matched control group at single site	$N = 58$ (29 in each group) Women with BMI >25 kg/m^2 undergoing IVF/ICSI for first time	120 mg orlistat thrice daily from day 1 in previous cycle until day of embryo transfer	29 patients with matched age and BMI who were undergoing	From day 1 of previous menstrual cycle until day of	Clinical pregnancy rate of orlistat group was significantly higher than the control group (59.46% vs. 39.47%), but there was no significant difference in the live	Orlistat increased the clinical pregnancy rate

TABLE 2 (Continued)

Citation (first author, year and country)	Study design	Population and sample size (including eligibility, age, BMI and co-morbidities)	Drug type and dosage	Control group	Duration of intervention	Main outcomes	Conclusion
		Orlistat group at baseline[a]: Mean age (SD): 28.10 (4.5) Mean BMI (SD): 28.53 (2.63) 7 of 29 participants had PCOS		IVF/ICSI for first time	embryo transfer	birth rate between groups (54.05% vs. 36.84%)	
Totoian[b], 2016, Russia	No details (abstract only)	$N = 17$ BMI >30 kg/m^2	120 mg orlistat thrice daily	No control group	6 months	Orlistat resulted in 12.3% reduction of body weight and 13.3% reduction in BMI (13.3%). Normalisation of hormonal levels, menstrual cycle and ovulation was observed	Orlistat is effective in the treatment of women with obesity and menstrual cycle disorders
Wang, 2021, China	Randomised double-blind placebo controlled multisite trial	$N = 877$ (439 orlistat, 438 placebo) Women scheduled for IVF/ICSI aged 20–40 years and BMI >25 kg/m^2 Orlistat group at baseline[a]: Mean age (SD):30.52 (3.99) Mean BMI (SD):29.27 (3.00)	120 mg orlistat thrice daily, alongside daily multivitamins and lifestyle modification advice	Placebo tablets, alongside daily multivitamins, and lifestyle modification advice	Between 4 to 12 weeks and stopped the day of embryo transfer	387 participants in each group underwent IVF cycle. No significant difference between groups for live pregnancy rate, rates of conception, clinical pregnancy, or pregnancy loss Significantly higher birth weight noted in orlistat group (3.487 kg vs. 3.285 kg) Mean weight change was greater in orlistat group compared to placebo (−2.49 kg vs 1.22 kg)	Orlistat treatment prior to IVF did not improve the live birth rate, although was beneficial for weight reduction

Abbreviations: BMI, body mass index; FSH, follicle stimulating hormone; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilisation; LH, luteinising hormone; PCOS, polycystic ovarian syndrome; SD, standard deviation; SHBG, sex hormone binding globulin.

[a]Was not significantly different from control group at baseline.

[b]Article in Russian, only abstract available.

addressing contraception and the need for further research to be conducted in women of reproductive age.

Nuako et al.[32] summarised the pharmacological treatment of obesity in reproductive-aged women, discussing several approved weight loss medications available in the USA, of which liraglutide, semaglutide and orlistat were three. The review by Jensterle et al.[34] explored the physiological mechanisms of GLP-1 RAs on reproductive health. Gill and Mackey[14] focused on the role that obstetrician-gynaecologists can play in supporting their patients in initiation of and adherence to GLP-1 RAs. Two further reviews from 2023 were identified in the updated systematic search in January 2024.[31,35] Of note, Goldberg et al.[31] raised the issue of GLP-1 RAs in the context of weight regain and oocyte cryopreservation, two topics not discussed in detail by other included articles.

3.6 | Systematic reviews

Two systematic reviews were identified as eligible for inclusion in this scoping review. Muller et al.[12] undertook a systematic review of the effects of GLP-1 RAs during pregnancy and lactation on offspring outcomes, in both human and animal studies. Their search did not yield any relevant primary studies on women without PCOS or diabetes. Similarly, Taghavi et al.[36] conducted a Cochrane review on pharmacological and non-pharmacological strategies for women with obesity and subfertility and their search did not yield any primary studies eligible for inclusion in this scoping review. Of the 10 included studies in the Cochrane review, only one study included liraglutide[38]; however, this was in women with PCOS, in combination with metformin.

3.7 | Published protocols

A protocol for a planned pregnancy registry study about semaglutide was identified. At the time of writing, the study had yet to start recruitment.[37] The study, funded by pharmaceutical company Novo Nordisk, aims to evaluate the safety of exposure to semaglutide during pregnancy and will collect data at three sites in USA, Spain, and the UK. The primary outcome is the rate of major congenital malformation and infants will be followed up until 12 months of age.

There were three registered systematic review protocols on PROSPERO,[39–41] all of which will only include RCTs. Details of all four protocols are shown in Table 3.

4 | DISCUSSION

This scoping review aimed to investigate what is known about the use of weight loss medication in women of childbearing age in relation to fertility and reproductive health outcomes. The systematic search focused on studies about the three medications licenced in the UK as of January 2024 (orlistat, liraglutide and semaglutide) in reproductive-aged women without PCOS or diabetes. Although a small number of trial studies were identified about the use of orlistat preconceptionally, no studies with primary data about the use of GLP-1 RAs were identified that met the inclusion criteria of the review. The number of recent narrative reviews underlines this as a very current topic that is gaining awareness and raising concerns amongst clinicians and researchers in reproductive health. Of note no qualitative studies about the use of GLP-1 RAs were identified, meaning there is little known about the experiences and needs of those who may be using these medications for overweight/obesity and fertility indications.

Overall, the six studies with primary data about orlistat were heterogenous in design, geographical setting, and sample size, making comparisons and definitive conclusions difficult to form. The largest of the studies[27] ($n = 877$), a multisite RCT based on China which gave orlistat before fertility treatment, did not find an improvement in the live birth rate, although orlistat was beneficial for weight reduction. The rate of obstetric and perinatal complications was also similar between groups. However, the authors report the high level of deviation from protocol (>10% participants) and in some situations the short duration of orlistat usage (~4 weeks) as important limitations to consider. A substantial number of participants were understandably unwilling to delay initiating fertility treatment to take orlistat for a prolonged period. However, the authors explain the demand for rapid fertility treatment is reflective of real-life practice and highlight that the use of orlistat (or other weight loss modality) needs to be implementable and acceptable to patients seeking to conceive within reasonable time constraints.[27] Similarly, the FIT-PLESE study[28] concluded that in women with both obesity and unexplained infertility, an intensive preconception lifestyle intervention including orlistat, with an average weight loss of 7%, did not improve the rate of having a healthy live birth or any live birth compared to an activity-based intervention that was weight neutral. There was also no improvement in pregnancy rates or time to pregnancy, which were unexpected despite improved cardiometabolic indicators after weight loss. The non-significant trend of higher miscarriage in the orlistat group was noted to occur after implantation and possibly attributed to decreased long-chain polyunsaturated fatty acid absorption,[28] underlying the importance of patients having dietary advice which may include supplementation. Although the other three orlistat studies did show improvements in reproductive hormone levels and markers of ovulation,[25,26,29] these were all studies with small sample sizes and quality of the studies was not appraised due to the nature of this review.

Orlistat preceded GLP1-RAs, having been available in the United States and Canada since 1999[42] and in Australia since 2000.[43] Although it has been licenced for weight loss since 2010 in the UK, primary care prescribing data indicates it has been on a long-term downward trend from 1 087 000 items per calendar year in 2010 to 294 000 items in 2020.[44] This may be due to its known gastrointestinal side effects and non-response rate in some individuals.[45] Its efficacy is also lower than the newer available weight loss medications, with research from several years ago showing greater mean weight loss with liraglutide compared with orlistat (mean difference, 3.7 kg at 1 year).[46] Indeed the Canadian guidelines on pharmacotherapy for

TABLE 3 Details of systematic review and trial protocols.

First author, country and year of registration	Population of interest (including inclusion criteria for age, BMI and co-morbidities, where specified)	Intervention/exposure of interest (Drug type and dosage if stated)	Comparator	Outcomes	Additional comments
Ruiz-Gonzalez, Spain, 2022	Women at fertile age with overweight or obesity	Non-surgical interventions (exercise, diet, and pharmacological strategies) for weight reduction and fertility	Placebo or no intervention	Circulating levels of testosterone, androstenedione, dehydroepiandrosterone-sulphate, progesterone, oestradiol, FSH, LH and free androgen index	RCTs only Articles published in English from inception until January 2022
Ma, China, 2022	Infertile women scheduled for IVF/ICSI cycle were eligible for enrolment if aged 20–40 years had a BMI ≥25 kg/m^2	Weight loss measures, including medications	Women with obesity undergoing IVF/ICSI who do not have weight loss intervention before pregnancy	Primary outcome: Live birth rate Secondary outcomes: Pregnancy rate, abortion rate, pregnancy complications	RCTs only
Guo, China, 2023	Participants with infertility, defined by the American Society of Reproductive Medicine, and BMI ≥25 kg/m^2	Lifestyle interventions or drugs like orlistat. Studies with bariatric surgery were not included	Usual infertility care	Primary outcomes: pregnancy rates and live birth Secondary outcomes: weight/BMI change, miscarriage, reproductive hormone levels including FSH, LH and SHBG; pregnancy complications including preeclampsia, gestational diabetes mellitus and haemorrhage, hypertension rates	RCTs only, published until October 2022, no language restrictions
Novo Nordisk, Multisite study in USA, Spain and UK, 2023	Pregnant females aged 15–50 who are exposed to semaglutide 2.4 mg during pregnancy for the treatment of obesity/overweight with ≥1 weight-related comorbid condition	Exposed to at least one dose of semaglutide at any time during pregnancy	Pregnant women with obesity/overweight with ≥1 weight-related comorbid condition at conception not exposed to semaglutide or other GLP-1 RAs during pregnancy	Primary outcome: rates of major congenital malformation Secondary outcomes: rates of minor congenital malformation, pre-eclampsia, eclampsia, spontaneous abortion, stillbirth, elective termination, preterm delivery, small for gestational age, postnatal growth deficiency, and infants with developmental delay. Infant outcomes will be assessed throughout the infant's first year of life, with active data collection by the registry occurring at 4 and 12 months after delivery	Observational prospective pregnancy registry study. Study start date July 2023, expected completion date December 2032

Abbreviations: BMI, body mass index; IVF, in vitro fertilisation; ICSI, intracytoplasmic sperm injection; FSH, Follicle stimulating hormone; GLP-1RA, glucagon-like peptide-1 receptor agonist; LH, luteinising hormone; PCOS, Polycystic ovarian syndrome; SHBG, sex hormone binding globulin.

obesity management explicitly state: 'The modest weight loss with orlistat above placebo, as well as its frequent gastrointestinal side effects, limit its use as therapy for obesity management'.[47] Therefore, the application of the findings of the orlistat studies identified in this review[27,28] to current practice in the UK is therefore limited, given the licencing of newer potentially better tolerated and more effective pharmacological options in the form of GLP-1 RAs.[10,48] Given that 64% of the adult population in England are living with overweight/obesity,[49] demand for GLP-1 RAs nationally already vastly outstrip supply, with shortages also noted internationally.[50] Indeed, a recent analysis of routinely collected primary care data in England reported that only 3.13% ($n = 56\,783$) of the >1.8 million adults with overweight/obesity were referred to weight management services.[5] The proportion of patients referred to multidisciplinary weight management clinics, where GLP1-RAs will be prescribed,[10] is smaller again.

Coupled with this, women with obesity referred for assisted reproductive technology may find restrictions are imposed until weight loss has occurred.[51] Nuako et al highlight that reproductive-age women face overlapping systems of stigma: from both weight-related stigma and infertility-related stigma.[32] These factors combined may drive those who have the financial means to source and pay for GLP-1 RAs online without a prescription, which raises concerns as there is no individualised healthcare professional monitoring. It is plausible that those taking unregulated medications purchased online without a prescription may not be receiving any advice for the need for contraception. In those with PCOS, meta-analyses of 11 trials have indicated an improvement in menstrual regularity and natural pregnancy rate with the use of GLP-1 RAs.[15] Potentially weight loss through the use of GLP-1 RAs in those without PCOS may also improve menstrual regularity and anovulatory dysfunction, leading to unintended pregnancies. This improvement in reproductive hormones and increase in fertility has been extensively reported post-bariatric surgery,[52] prompting international guidelines to be developed.[53] This review did not identify any studies that examined off-script sourcing of GLP-1 RAs and/or evaluate the role of healthcare professional supervision, although Gill and Mackey highlighted the role of the obstetrician/gynaecologist in initiating and monitoring patients on GLP-1 RAs.[14]

The teratogenic risk of GLP-1 RAs in animal studies is well established, with evidence of reduced fetal weight, reduced embryonic survival and major skeletal malformations in rat, mouse and rabbit models associated with decreased maternal food consumption and weight.[12] With a lack of evidence as to whether liraglutide and semaglutide transfer across the placenta and whether humans are similarly affected,[12] contraception is recommended for those taking either liraglutide or semaglutide,[8,9] although the timeframe is not always clear. In Europe and the United States, of note, GLP-1 RAs are a classified as a "category C" drug for pregnancy, by the European Medicines Agency and Food and Drug Administration respectively. This means if administered in women preparing for pregnancy, a washout period should be included. Due to the long half-life of semaglutide, which is self-administered as a once-weekly subcutaneous injection, a washout period of 8 weeks is recommended before people try to conceive. There is no official recommendation for the timing of discontinuation of liraglutide prior to conception. As it has a shorter half-life than semaglutide, it has therefore been suggested that prescribers should counsel to discontinue liraglutide 10–14 days prior to attempting to conceive.[31] In terms of suitability of different contraceptives, liraglutide and semaglutide have[8,9] not been demonstrated to alter absorption of oral contraceptives. However, tirzepatide, a weight loss medication soon to be, available in the United States since November 2023,[54] soon to be available in the UK, may reduce the efficacy of oral hormonal contraceptives and a therefore barrier method is recommended upon initiating therapy.[55] In their narrative review, Nuako et al.[32] emphasise discussing long-acting reversible options including intra-uterine devices or hormonal implants, to enable women to control the timing of pregnancies while taking GLP-1 RAs or considering their use. Weight regain post-cessation of GLP1-RA is well established,[56] however, the extent of weight regain during the wash-out phase prior to pregnancy is not known, nor how this may influence gestational weight gain and perinatal outcomes,[31,57] another factor that should be explained by practitioners.

It is relevant to note that in the seminal STEP 8 trial ($n = 388$), which compared the effectiveness of semaglutide and liraglutide, 78.4% of participants were female.[56] Similarly, in the SCALE trial ($n = 3731$) which evaluated the effectiveness of liraglutide, 78% were women.[58] This suggests a higher demand for weight loss medication in women more so than men, reflective of men's engagement in weight loss services more generally.[59] However, the mean age range of participants in these studies was 49 and 45 years, respectively. Nuako et al.[32] surmise that as many of the existing studies on weight loss pharmacotherapy are based on populations aged >45 years, reproductive health may have been perceived as not relevant. This is in parallel with policy reports demonstrating that pregnancy research is allocated only 2.4% of all direct, non-industry health research, significantly less than other conditions.[60] In contrast, litigation claims related to pregnancy, which can include claims related to medication, are around 50 times current pregnancy research spend. As such, research on medications safe to take during pregnancy is one of the top five research priorities. Muller et al.[12] reviewed studies on a range of GLP-1 RAs available internationally, including exendin-4, exenatide, albiglutide, dulaglutide and lixisenatide, in addition to semaglutide and liraglutide. They argue that data on the placental transfer and the degree in which the neonatal adverse effects of GLP-1 RAs can be ascribed to maternal malnutrition could be assessed in multiple animal models. They recommend future studies to report maternal and treatment characteristics including trimester of exposure more thoroughly and that long-term follow-up data on neonatal outcome after maternal exposure is needed. The identified pregnancy registry study about semaglutide exposure intends to follow up any offspring for 12 months,[37] which may not be sufficient enough to identify long-term outcomes.

4.1 | Strengths and limitations

The methods used in this scoping review were rigorous and transparent and followed a defined methodology[21,61] with systematic

searches undertaken and screening undertaken by two independent reviewers. As the scoping method seeks to identify all relevant literature regardless of study design, its reach is comprehensive. However, since quality assessment does not form part of the scoping methodology, it does not necessarily identify whether the research itself is poor quality or determine whether particular studies provide robust findings.[20,22] As it is already known that liraglutide and semaglutide have proven efficacy in weight loss[56,58] and improving endocrine biomarkers in those with PCOS,[15] we specifically chose to include only studies focused on participants who did not have PCOS. However, we acknowledge the overlap between obesity and PCOS, especially in those seeking fertility treatment, meaning obesity in the absence of PCOS is less often investigated in reproductive health studies. Focusing the search on the three currently licenced medications in the UK potentially limits the generalisability of the findings, however the same medications are also licenced internationally, and results are applicable to other regions. We did not search for studies that explored the effects of these three medications on lactation, as this was outside the scope of the research question. Similarly, studies about male fertility were not considered; however, a recent narrative review highlighted a similar lack of knowledge on long-term outcomes and a need for further clinical trials to clarify potential benefits for male reproductive parameters.[62]

5 | CONCLUSION

The use of orlistat preconceptionally did not demonstrate any benefit on live birth rates, despite improvements in reproductive hormones and weight. There is an absence of primary data about the role of GLP-1 RAs on the reproductive health outcomes of women of childbearing age without PCOS, including an absence of qualitative research. It remains unclear whether it is beneficial for women with overweight/ obesity who might become pregnant in the future to use them and if so when is the optimal preconceptional timing to start drug treatment. The contraindication of these medications during pregnancy is an obvious barrier limiting the evaluation of their use in those planning pregnancy. However, with appropriate and timely contraceptive counselling, women of reproductive age should not be disadvantaged in accessing effective weight loss medications. Future research should investigate safety before, during and after pregnancy, including short- and long-term effects on reproductive health and pregnancy outcomes.

AUTHOR CONTRIBUTIONS

Study conceptualisation: KM, JS. Methodology: KM, JS, RA, JG. Searches: KM, RA. Screening: KM, RA, JS. Data extraction: KM, JS, RA. Writing—original draft preparation: KM. Writing—review and editing: KM, RA, JG, JP, JS.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest related to this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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