



Interventions to improve insulin resistance for the prevention of endometrial cancer

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Interventions to improve insulin resistance for the prevention of endometrial cancer (Protocol)

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[Intervention Protocol]

Interventions to improve insulin resistance for the prevention of endometrial cancer

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the safety and effectiveness of interventions to improve insulin resistance for the prevention of atypical endometrial hyperplasia or endometrial cancer, or both.

BACKGROUND

Description of the condition

Cancer of the womb (uterus) is the most common cancer affecting the female reproductive system in the developed world. Most womb cancers arise from abnormal growth of the womb lining (endometrium) and are termed endometrial cancer. Endometrial hyperplasia is a thickening of the womb lining, which can progress to endometrial cancer, if untreated. Worldwide, endometrial cancer affects 382,000 women per year (Globocan 2019), including over 9000 women in the UK. Its incidence rates have increased by almost three-fifths (57%) in the UK since the early 1990s, with similar trends reported globally (Lortet-Tieulent 2018). Most women diagnosed with endometrial cancer are postmenopausal; 93% of those diagnosed in the UK between 2014 and 2016 were over the age of 50 (CRUK 2019). Increasingly, however, a greater number of younger premenopausal women are being diagnosed with the disease (Unzurrunzaga 2019).

Most of the increase in incidence is due to low-grade Type 1 cancers. These are largely caused by an excess of the sex hormone, oestrogen, unopposed by progesterone (Kaaks 2002). Other risk factors include advancing age, insulin resistance and diabetes (Friberg 2007; Zhang 2013). The common link for all these risk factors is obesity. Worldwide, the prevalence of obesity (body mass index (BMI) > 30 kg/m²) has doubled in the last 30 years. Of the 20 most common tumour types, endometrial cancer has the strongest association with obesity, with a 5 kg/m² increase in BMI being associated with a 60% increase in endometrial cancer risk. As the risk rises exponentially, a woman with a BMI of 42 kg/m² has a nine-fold higher chance of developing endometrial cancer compared with a woman with a BMI of 22 kg/m² (Bhaskaran 2014; Renehan 2008). Several different theories have been proposed to explain the link between obesity and endometrial cancer. These include an excess of endometrial pro-growth factors, including oestrogen, increased inflammation and insulin resistance.

Insulin is a hormone that helps the body process glucose (sugar). Insulin resistance occurs when target tissues (including liver, skeletal muscle and fat) do not respond appropriately to insulin and cannot break down glucose in the blood (Lebovitz 2001). If the pancreas is unable to produce enough compensatory insulin to counteract this, chronic hyperglycaemia (high glucose) and hyperinsulinaemia (high insulin) lead to the development of type 2 diabetes mellitus (T2DM). In obese people, dysregulation of signalling proteins (including tumour-necrosis factor- α (TNF- α) and adiponectin) lead to chronic inflammation and insulin resistance (Calle 2003; Kaaks 2002).

Multiple studies have found an association between prolonged high insulin levels and an increased incidence of cancer, including colorectal, hepatic, pancreatic, breast and endometrial cancers (Friberg 2007; Huxley 2005; Larsson 2005; Michels 2003; Wang 2012). Women with T2DM have a two-fold increased risk of endometrial cancer compared with women without diabetes (Friberg 2007). Whilst most obese women are insulin resistant (Abbasi 2002), insulin resistance and diabetes are additional independent risk factors for endometrial cancer. Insulin resistance alone continues to increase the risk of endometrial cancer, even after adjusting for the effect of obesity (Friberg 2007; Lucenteforte 2007).

Insulin and its related protein, insulin-like growth factor-1 (IGF-1), play important roles in driving proliferation (increased cell numbers), differentiation (changing of one cell type to another) and metabolic (chemical) activity within the normal endometrium (Merritt 2016). They do this by binding to the insulin and IGF-1 receptors, leading to activation of growth signalling pathways, such as PI3K/AKT/mTOR [phosphoinositide 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR)] and mitogen-activating protein kinase (MAPK) (Cantrell 2010; Nagamani 1998; Renehan 2006). A rise in insulin and IGF-1 levels is associated with endometrial growth, thus increasing the risk of abnormal endometrial cells and, eventually, cancer formation. Increased expression of insulin and IGF-1 receptors, and over-activation of the associated growth signalling pathways, have been reported in endometrial hyperplasia (McC Campbell 2006), and endometrial cancer (McC Campbell 2010; Wang 2013).

Early-stage endometrial cancer is treated surgically by removing the uterus, fallopian tubes and ovaries. In women with aggressive or advanced disease, this is followed by radiotherapy or chemotherapy, or both. When endometrial cancer is diagnosed in women of child-bearing potential, these treatments result in infertility, which can be devastating to those who have not completed their families. Most women with endometrial cancer are diagnosed with early stage (FIGO stage I and II) curative disease. Obesity, however, can make surgery more challenging and present increased complications and healthcare costs. (Suidan 2017).

Interventions to prevent endometrial cancer, therefore, would have significant benefits for both the woman and for healthcare systems as a whole. In high-risk women with a familial predisposition for endometrial cancer (Lynch Syndrome), identification of the condition allows familial-based genetics follow-up and access to cancer surveillance programmes (e.g. camera assessments and biopsies of the womb lining). Risk-reducing surgery, in the form of a hysterectomy and removal of tubes and ovaries after the family is complete, is an established method of preventing endometrial cancer in these women.

Some women are diagnosed with endometrial hyperplasia, a precursor lesion, which, if left untreated, can lead to endometrial cancer. This risk is highest in women with atypical endometrial hyperplasia, where the thickening is accompanied by abnormal cell changes (Kurman 1985; Lacey 2008). Atypical hyperplasia in women who have completed their families is treated surgically, with a hysterectomy, removing the womb and cervix (RCOG/BSGE 2016). Women wishing to retain their fertility, or those unfit for surgery, can be treated by insertion of a progesterone-releasing hormone coil (Mirena coil), oral progestogens and weight loss interventions. Oral progesterones have a number of side-effects, including headaches, mood changes and acne. Longer-term progesterone treatment increases the risk of a thromboembolic event (venous blood clots) and breast cancer (BNF 2019), so may not be suitable for all women. In atypical endometrial hyperplasia, disease regression rates (i.e. resolution of atypical changes) of up to 86% have been reported (Gallos 2012), however, significant disease recurrences are also recognised.

In the general population, prevention strategies are based on targeting established risk factors. Manipulation of sex hormones, including oral, injectable and intrauterine progestins, has been shown to reduce endometrial cancer risk (Jareid 2018). The combined oral contraceptive pill is also associated with a

reduction in the lifetime risk of endometrial cancer (Iversen 2017). Unfortunately, in obese women with a BMI greater than 35 kg/m², the risks of thromboembolic events outweighs the potential benefit (UK MEC 2009).

Another potential intervention is to specifically focus on a driver of endometrial carcinogenesis (cancer development) in women who are at increased risk; for example, by improving insulin resistance in women with diabetes or obesity, or both. Women with polycystic ovary syndrome (PCOS), a metabolically-driven gynaecological disorder, have a three-fold increased risk of developing endometrial cancer compared to women without PCOS (Haoula 2012). This increase is likely to be driven by a combination of insulin resistance and unopposed oestrogen, leading to reduced or absent menstruation. As insulin resistance is thought to be a key player in the development of PCOS, studies have tested the effect of metformin in the treatment of endometrial hyperplasia. A recent Cochrane Review concluded that the existing evidence is insufficient, and that further research using robust, adequately-powered randomised controlled trials is needed to answer this clinical question (Clement 2017).

Cancer prevention interventions require two key attributes: the ability to predict and identify high risk individuals, and a means of assessing the efficacy of the intervention. Measuring the response in endometrial cancer prevention studies can be problematic. These studies require a large number of subjects and a prolonged follow-up period to detect an absolute decrease in the incidence of cancer. As this approach is often prohibitively expensive, investigators have used endometrial tissue proliferation biomarkers (e.g. the Ki-67 protein) as a surrogate for assessment of response (Kitson 2017). Alternatively, regression of endometrial hyperplasia histology towards normal histology could be used as a measure of response.

Description of the intervention

This review will focus on interventions designed to improve insulin resistance as the primary goal, and will include pharmacological, non-pharmacological and surgical interventions, used alone or in combination. Pharmacological interventions include drugs that act to improve insulin resistance (e.g. metformin, sulphonylureas, thiazolidinediones, insulin), and drugs that induce weight loss through reduction of fat absorption (e.g. orlistat), or appetite suppressants. Non-pharmacological or 'lifestyle' interventions are those which aim to increase physical activity and reduce calories, including diet, exercise and psychological management (examples). Surgical interventions include weight loss (bariatric) surgery, such as procedures designed to limit food intake (e.g. gastric banding), cause malabsorption (e.g. intestinal bypass), or both.

How the intervention might work

Reducing insulin resistance may prevent the development of endometrial cancer by changing the hormonal profile in women at risk. Insulin breaks down glucose for use as an energy source, and maintains blood glucose in a stable range. Insulin resistance in the target tissues (e.g. skeletal muscles, liver cells) leads to an increase in insulin production from the pancreas, to maintain normal glucose levels. Eventually, the pancreas fails to produce sufficient insulin to counteract the high glucose levels, resulting in hyperglycaemia (high blood glucose) and hyperinsulinaemia (high

insulin). Hyperglycaemia due to T2DM may facilitate cancer cell growth through the following mechanisms.

Insulin from the pancreas acts on the liver to increase the production of growth factors (IGF-1/2) and to decrease growth-factor neutralisers (IGF-binding proteins 1 and 2). This results in an excess of growth factors (insulin and/or IGF1/2), which bind to the insulin receptor (IR) and IGF-1 receptors (IGF1R) to activate cancer proliferation pathways [phosphoinositide 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) and Ras-Raf-MAPK]. The PI3K-AKT-mTOR and Ras-RAF-MAPK pathways are implicated in the development of endometrial cancer. Activation of these pathways initiates a cascade of signalling events, which promote cellular growth, the development of abnormal blood vessels (angiogenesis) and abnormal migration of cells.

Higher levels of IGF-1 have been reported in overweight individuals (Crowe 2011). Even in people of who are not overweight, higher levels correlate with an increased risk of breast, prostate and colorectal cancers, and increased levels of the target receptors (IGF-1 receptor) have been observed (Yu 2000). In these cancers, persistently elevated insulin and/or IGF1/2 are thought to increase tumour growth signalling and metastases. In a further study of women with a disordered proliferative endometrium, endometrial hyperplasia and endometrial cancer, Shan 2014 found insulin resistance and high insulin levels to be key events early in abnormal endometrial growth, and may even be the initiating events in the development of endometrial cancer.

Thus, metformin and other drugs that increase the body's response to insulin have been proposed as potential interventions. Metformin is one of the most widely used oral treatments for T2DM, and is used for PCOS, infertility, obesity and hirsutism (excess hair growth). Metformin is thought to reduce cancer growth in two ways. Firstly, it stops glucose production in the liver, resulting in a decrease in compensatory insulin production and lower levels of insulin in circulation. Secondly, metformin can act at a cellular level through the mitochondria. Mitochondria are found in most cells and control cellular respiration and energy production. Metformin acts to activate the signalling protein AMP-activated protein kinase (AMPK), which directly inhibits the PI3K-AKT-mTOR cancer proliferation pathway.

Some epidemiological studies have reported that people with diabetes who take metformin have a substantially lower cancer burden than people with diabetes treated with other agents (DeCensi 2010; Evans 2005; Gandini 2014). A meta-analysis of 11 studies (involving 766,926 participants) found that metformin use was associated with a 13% reduction in endometrial cancer in women with diabetes (Tang 2017). Human, animal and laboratory models have shown metformin to have direct anti-cancer effects. In rats, it has been shown to reduce endometrial hyperplasia caused by oestrogen (Tas 2013), and reduce activation of the mTOR cancer proliferation pathway (Erdemoglu 2009). Small clinical trials and case reports have demonstrated resolution of simple and atypical hyperplasia (excess cell growth with abnormal cells) following treatment with metformin and/or rosiglitazone, a thiazolidinedione (oral diabetes treatment) (Legro 2007; Session 2003; Shen 2008). The evidence for the role of metformin, however, can be conflicting. An Italian case-control study, which compared 376 diabetic women with endometrial cancer and 7485 age-matched diabetic controls, found no significant association between metformin, sulphonylureas, insulin or other

anti-diabetes medications and the risk of endometrial cancer. These discrepancies in the studies' findings could be explained by differences in study design, such as size, indication for metformin use and the dose and durations of treatment. On balance, however, the data suggest that the role of insulin resistance and hyperglycaemia in endometrial cancer merit further investigation.

Public health interventions that decrease the overall prevalence of obesity could have an even greater impact on decreasing endometrial cancer incidence. Intentional weight loss, particularly in women who were obese at baseline, has been reported to lower the risk of endometrial cancer (Luo 2017). These findings are consistent with reports that sustained weight loss after bariatric (weight-loss) surgery has been associated with lower endometrial cancer risk in severely obese women (MacKintosh 2019; McCawley 2009; Sjostrom 2009). Improvements in insulin resistance (as measured by the Homeostatic Model of Insulin Resistance (HOMA-IR), are seen shortly after surgery and, indeed, before any significant weight loss has occurred. This suggests that the metabolic changes following surgery are important, particularly improvement in insulin resistance (Arora 2015; Ward 2014). Sustained weight loss is associated with improvement in both HOMA-IR and HbA1C (glycated haemoglobin, a measure of blood sugar control) (Parikh 2014). It is likely that both non-pharmacological and surgical interventions which lead to weight loss will have a favourable effect on improving insulin resistance.

Why it is important to do this review

The burden of endometrial cancer has increased in the developed world, and is expected to increase in lower income countries as obesity becomes more prevalent (Arnold 2015). Prevention strategies must include targeting the key mechanisms that drive endometrial cancer development. There is a bulk of evidence to support a causative role for insulin resistance in endometrial cancer.

This theme ranked as the most important endometrial cancer research priority for patients, carers and healthcare professionals in a recently completed Womb Cancer Priority Setting Partnership (Wan 2016). This review will establish whether the evidence already exists, or whether well-designed randomised controlled trials are required to provide it. This review will set the scene for high-quality research to assess the feasibility, effectiveness and cost-effectiveness of interventions to reduce insulin resistance (including physical activity and dietary interventions, bariatric surgery or drugs (e.g. metformin, thiazolidinediones, sulphonylureas, insulin) for the prevention of endometrial cancer, in both at-risk groups (women with obesity, insulin resistance and type 2 diabetes, PCOS or atypical hyperplasia) and the general population. There have been no previous Cochrane Reviews on this topic.

OBJECTIVES

To determine the safety and effectiveness of interventions to improve insulin resistance for the prevention of atypical endometrial hyperplasia or endometrial cancer, or both.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), which are considered the highest level of clinical trial evidence. We will include studies reported as full text, those published as abstract only, and unpublished data, to ensure that we incorporate all relevant trials.

Types of participants

We will include trials that enrol women ≥ 18 years of age, who are diagnosed with insulin resistance, or T2DM, and who have not had a hysterectomy (so remain at risk of developing endometrial cancer).

To be consistent with changes in classification and diagnostic criteria of insulin resistance and T2DM over the years, we require participants' diagnoses to reflect the standard criteria valid at the beginning of the trial (e.g. ADA 2003; ADA 2008; ADA 2019; Diabetes UK 2019; NICE 2017; WHO 1998; WHO 2011). Ideally, the trials will have described the diagnostic criteria, but, if not, it may be necessary to use the trial authors' definition of insulin resistance or T2DM. If the publication does not describe the diagnostic criteria, we will contact the study authors to request raw data, and will use the cut-offs described below.

We will accept a diagnosis of insulin resistance as an HbA1C of 42 mmol/L to 47 mmol/L or 6.0% to 6.4%, a fasting plasma glucose of 5.5 mmol/L to 6.9 mmol/L (NICE 2017), or an oral glucose tolerance test (OGTT) result of 140 mg/dL to 199 mg/dL (ADA 2019).

We will accept a diagnosis of T2DM as an HbA1C of $\geq 6.5\%$ (WHO 2011), a fasting plasma glucose of ≥ 7.0 mmol/L (Diabetes UK 2019), or an OGTT result of ≥ 200 mg/dL (ADA 2019).

If authors are unable or unwilling to provide these data, we will exclude the study from the systematic review and meta-analysis.

We will exclude women with a histological diagnosis of endometrial cancer.

Types of interventions

We will include studies that report interventions designed to improve insulin resistance as one of their primary or secondary stated outcomes, in any healthcare setting. These will include:

- pharmacological interventions to improve insulin resistance (such as, but not limited to, metformin, sulphonylureas, thiazolidinediones, insulin) and promote weight loss (such as, but not limited to, appetite suppressants, including serotonin receptor antagonists, or drugs that cause fat malabsorption);
- non-pharmacological interventions, including supervised dietary and physical activity regimens;
- surgical interventions to promote weight loss (gastric band, sleeve or bypass procedure).

We will compare these interventions with any other intervention, usual care, or placebo.

Types of outcome measures

We will describe primary and secondary outcome measures in terms of the effect of the intervention on improving insulin resistance, and the incidence of a new diagnosis of atypical hyperplasia and/or endometrial cancer, adverse events and weight loss. These are important measures that will help guide whether these interventions should be included in routine clinical care. Inclusion of these outcomes in the study design will not determine eligibility of the trial for this review.

Primary outcomes

The primary outcomes of this review will be:

- incidence of a new diagnosis of atypical endometrial hyperplasia or endometrial cancer, or both, between randomisation and the end of the trial period; number of participants diagnosed following randomisation per number of participants studied
- regression of a histological diagnosis of atypical endometrial hyperplasia to normal histology and/or non-atypia .

Secondary outcomes

Secondary outcomes will include:

- decrease in measures of glycaemic control since randomisation; measured as a decrease in HbA1C, fasting plasma glucose or HOMA-IR (continuous variables);
- change in physical activity levels between randomisation and the end of the study, as determined by individual studies; physical activity could be assessed using objective measures (e.g. pedometers), or more subjective tools (e.g. diary, self-reported);
- weight loss; amount of weight lost between randomisation and end of study; measured by body mass indices (body mass (kg), BMI (kg/m²);
- changes in histological measures of endometrial proliferation, including Ki-67 expression; measured as determined by included studies;
- frequency of serious adverse events, of any nature; defined as Grade 3,4 or 5 events, according to the Common Terminology Criteria for Adverse Events (CTCAE 2017).

Search methods for identification of studies

We will impose no language restrictions on our searches. If necessary, we will have studies translated.

Electronic searches

We will search the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, latest issue);
- MEDLINE Ovid SP (1946 to present);
- Embase Ovid SP (1980 to present).

Appendix 1 shows the MEDLINE search strategy. We will adapt this for other databases accordingly.

We will search the following registers for ongoing clinical trials (2000-present):

- International Standard Randomised Controlled Trial Number (ISRCTN) metaRegister of Controlled Trials (www.isrctn.com/)
- www.controlled-trials.com/rct
- Physicians Data Query (www.cancer.gov/publications/pdq)
- www.nci.nih.gov
- www.clinicaltrials.gov

Searching other resources

We will handsearch the citations lists of included studies and previous systematic reviews, and contact experts in the field to identify further reports of trials. Where we require additional information, we will contact the principal investigator of the trial.

We will handsearch the reports of conferences in the following sources:

- *Gynecologic Oncology* (Annual Meeting of the American Society of Gynecologic Oncology);
- *International Journal of Gynecological Cancer* (Annual Meeting of the International Gynecological Cancer Society);
- *British Journal of Cancer*;
- NCRI Cancer Conference;
- British Obesity & Metabolic Surgery Society Annual Scientific Meeting;
- International Federation for the Surgery of Obesity and Metabolic Disorders endorsed meetings;
- Diabetes UK Professional Conference;
- American Diabetes Association Scientific Sessions.

We will search for other conference abstracts and proceedings using Zetoc and WorldCat Dissertations.

We will include a narrative review of relevant non-randomised studies in the Discussion section of the review.

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved by electronic searching to a reference manager database (EndNote), and remove duplicates. Two review authors (VS and SK) will independently examine the remaining references. We will exclude studies that do not clearly meet the inclusion criteria, and obtain full-text publications of potentially relevant references. Two review authors (VS and SK) will independently assess the eligibility of the retrieved reports and publications. We will resolve any disagreement through discussion, or if required, we will consult a third person (MM). We will identify and collate multiple reports of the same study, so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

Two review authors (VS and SK) will independently extract study characteristics and outcome data from included studies onto prepiloted data collection forms. We will note in the 'Characteristics of included studies' table if the trial did not report outcome data in a usable format. We will resolve disagreements by consensus, or by involving a third person (MM). One review author (VS) will

transfer data into the Review Manager file ([Review Manager 2014](#)). We will double-check that data are entered correctly by comparing the data in the Review Manager file with the study reports. A second review author (SK) will spot-check study characteristics for accuracy against the trial report. If an included study has multiple reports, we will collate the available data to ensure maximum information yield, and prioritise the publication with the longest follow-up associated with our review's primary and secondary outcomes.

We will extract the following data.

- Author, year of publication and journal citation (including language)
- Country
- Setting
- Inclusion and exclusion criteria
- Study design, methodology
- Study population (total number enrolled; baseline participant characteristics: age, comorbidities, BMI, diagnosis of insulin resistance or T2DM, timing of intervention in relation to diagnosis of atypical endometrial hyperplasia or endometrial cancer (time-to-event))
- Intervention details (type of intervention; dose, route of administration; duration of treatment; additional information as appropriate)
- Comparison (nature of intervention; dose, route of administration; duration of treatment; additional information as appropriate)
- Duration of follow-up
- Outcomes: for each outcome, we will extract the outcome definition and unit of measurement (if relevant). For adjusted estimates, we will record variables adjusted for in the analyses. We will contact study authors to obtain unadjusted data where possible.
- Results: we will extract the number of participants allocated to each intervention group, the total number analysed for each outcome and the missing participants.
- Notes: funding for trial, and notable conflicts of interests of trial authors.

We will extract the results as follows:

- For dichotomous outcomes (e.g. incidence of atypical hyperplasia or endometrial cancer, adverse events, endometrial cancer-related deaths), if it is not possible to calculate a hazard ratio, we will estimate a risk ratio; we will extract the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint.
- For continuous outcomes (e.g. weight loss, change in measures of endometrial proliferation, measures of insulin resistance), we will estimate the mean difference between treatment arms and its standard error; we will extract the final value and standard deviation of the outcome of interest and the number of participants assessed at endpoint in each treatment arm at the end of follow-up.

If reported, we will extract both unadjusted and adjusted statistics. Where possible, we will extract data relevant to an intention-to-

treat analysis and analyse participants in the groups to which they were assigned.

We will note the time points at which outcomes were collected and reported.

Assessment of risk of bias in included studies

We will assess and report on the methodological risk of bias of included studies in accordance with the criteria outlined in the *Cochrane Handbook of Systematic Reviews of Interventions* ([Higgins 2019](#)). Two review authors (VS and SK) will independently apply the 'Risk of bias' criteria; we will resolve differences by discussion or involving a third review author (MM). Risk of bias will be assessed using the following Cochrane RoB 2.0 criteria ([Higgins 2019](#))

- Bias arising from the randomisation process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result.

We will assess risk of bias in each domain. An algorithm using a series of signalling questions with answers (yes, probably yes, no information, probably no, no) will determine the risk of bias (low risk, some concerns and high risk). Following grading of each potential source of bias, we will provide a quote from the study report and a statement to justify the judgement for each criteria.

We will summarise results in both a graph and a narrative summary. When interpreting treatment effects and meta-analyses, we will take into account the risk of bias for the studies that contributed to that outcome. Where information on risk of biases relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table. When analysing treatment effects, we will consider the risk of bias for the studies that contribute to the outcome.

Measures of treatment effect

We will use the following approach measure the effect of the treatment.

- For time-to-event data (i.e. incidence of atypical hyperplasia and/or cancer), we will use the hazard ratio if possible
- For dichotomous outcomes, we will analyse data based on the number of events and the number of people assessed in the intervention and comparison groups. We will use these to calculate the risk ratio (RR) and 95% confidence interval (CI).
- For continuous outcomes, we will analyse data based on the mean, standard deviation (SD), and number of people assessed for both the intervention and comparison groups, to calculate the mean difference (MD) between treatment arms with a 95% CI. If the trial reports the MD without giving the data for each group, we will use this to report the study results. If more than one study measures the same outcome using different tools, we will calculate the standardised mean difference (SMD) and 95% CI using the inverse variance method in [Review Manager 2014](#).

We will only undertake meta-analyses where this is meaningful, i.e. if the treatments, participants, and underlying clinical questions are similar enough for pooling to make sense. We will report skewed data as medians and interquartile ranges.

Unit of analysis issues

The unit of analysis will be the individual participant. Where a single trial reports multiple intervention arms, we will only include the relevant arms and the 'shared' comparison group will be divided equally between the number of treatment groups to avoid 'double-counting'.

Dealing with missing data

We will analyse and document the reasons for missing data. To obtain missing data, we will contact the study authors. We will report on loss to follow-up and use this data in our assessment of the risk of bias of studies. When these data are unavailable, we will not impute them.

Assessment of heterogeneity

Where studies are considered similar enough (in terms of participants, interventions, comparators and outcome measures) to pool data using meta-analysis, we will assess the degree of heterogeneity by visual inspection of forest plots, by estimation of the percentage of heterogeneity between trials which cannot be ascribed to sampling variation (the I^2 statistic; Higgins 2003), by a formal statistical test of the significance of the heterogeneity (the χ^2 statistic; Deeks 2001) and, if possible, by subgroup analyses. We will use the following I^2 statistic level as a guide to assess heterogeneity:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 70% to 100%: considerable heterogeneity.

If substantial clinical, methodological, or statistical heterogeneity is detected across the included studies, we will not report pooled results from a meta-analysis. Instead, we will use a narrative approach to data synthesis. In this event, we will investigate and report the possible clinical or methodological reasons for this.

Assessment of reporting biases

We aim to minimise reporting bias by searching systematically for all eligible studies, including unpublished data and ongoing clinical trials, and by not imposing any language restrictions. Updates of this review will manage the issue of time-lag bias.

If we identify more than 10 studies that investigate a particular outcome, we will examine funnel plots that correspond to the meta-analysis of this outcome to assess the potential for small study effects such as publication bias. We plan to assess funnel plot asymmetry visually, and if asymmetry is suggested by a visual assessment, we will perform a formal statistical test for asymmetry. (Egger 1997).

Data synthesis

If we identify a sufficient number of clinically similar studies to ensure meaningful conclusions, we will pool their results in meta-analyses using a random-effects model. Given the number of possible interventions that the included studies may use, we will only perform the following meaningful comparisons.

- Pharmacological interventions versus placebo or no treatment

- Non-pharmacological interventions versus placebo or no treatment
- Surgical interventions versus placebo or no treatment
- Pharmacological interventions versus non-pharmacological interventions
- Pharmacological interventions versus surgical interventions
- Non-pharmacological interventions versus surgical interventions

If any trials have multiple treatment groups, we will divide the 'shared' comparison group into the number of treatment groups in the comparison and treat the split comparison group as independent comparisons. If it is not possible to pool the data statistically in a meta-analysis, we will present the results in a narrative style, organised by intervention categories, according to the major types or aims of the identified interventions. Depending on the available research, we may explore the possibility of organising the data by population. Within the data categories, we will explore the main comparisons of the review.

'Summary of findings' table

We will present the overall certainty of the evidence for each outcome according to the GRADE approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity, such as directness of results (Langendam 2013; Schnemann 2011). We will create a 'Summary of findings' table (Appendix 2) based on the methods described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011a) and using GRADEpro GDT 2015... We will use the GRADE checklist and GRADE Working Group certainty of evidence definitions. We will downgrade the evidence from 'high' certainty by one level for serious (or by two for very serious) concerns for each limitation.

- High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

We will include these outcomes in the 'Summary of findings' table:

- incidence of endometrial cancer or atypical hyperplasia, or both;
- regression or resolution of histological atypia or cancer;
- improvement in measures of insulin resistance;
- physical activity;
- weight loss;
- change in measures of endometrial proliferation;
- frequency of adverse events.

If meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table format (Chan 2011).

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses for the following factors:

- BMI (using WHO categories i.e underweight <18.5kg/m², normal weight (18.5 to 24.9kg/m²), overweight (25.0 to 29.9kg/m²), obese (30 to 39.9kg/m²) and morbidly obese (>40kg/m²).
- Degrees of insulin resistance (Insulin resistance versus overt T2DM).

We will consider age, ethnicity and length of follow-up in the interpretation of any heterogeneity. We will use the formal test for subgroup differences in Review Manager 5 ([Review Manager 2014](#)), and base our interpretation on this.

Sensitivity analysis

If adequate data are available, we will perform a sensitivity analysis to compare studies with high and unclear risk of bias and low

risk of bias for attrition and outcome reporting, and allocation concealments (the latter is relevant only to pharmacological interventions).

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APPENDICES

Appendix 1. MEDLINE Ovid search strategy

1. exp Insulin Resistance/
2. Hyperinsulinism/
3. Glucose Metabolism Disorders/
4. (insulin resistance or insulin-resistance or IR or IGF* or insulin-like peptide* or ILP*).mp.

5. Metabolic Diseases/
6. exp Hypoglycemic Agents/
7. (hyperinsulin* or hyperglycem* or hypoglycem* or glucose* or metabol*).mp.
8. (Thiazolidinedione* or Glitazone* or Metformin* or Insulin* or Pioglitazone* or rosiglitazone* or troglitazone* or sulphonylurea* or Exenatide* or Liraglutide* or Glucagon like peptide* or Orlistat*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
9. Blood Glucose/
10. (blood glucose* or blood-glucose* or blood sugar* or blood-sugar*).mp.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp Endometrial Neoplasms/
13. (endom* adj5 (precancer* or pre-cancer* or pre cancer* or premalignan* or pre-malignan* or pre malignan* or cancer* or neoplas* or carcinom* or adenocarcinom* or malignan* or tumor* or tumour* or EIN or hyperplasia*)).mp.
14. ((uter* and lining) adj5 (precancer* or pre-cancer* or pre cancer* or premalignan* or pre-malignan* or pre malignan* or cancer* or neoplas* or carcinom* or adenocarcinom* or malignan* or tumor* or tumour*)).mp.
15. ((womb or corpus uter*) adj5 (precancer* or pre-cancer* or pre cancer* or premalignan* or pre-malignan* or pre malignan* or cancer* or neoplas* or carcinom* or adenocarcinom* or malignan* or tumor* or tumour*)).mp.
16. 12 or 13 or 14 or 15
17. 11 and 16
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomized.ab.
21. placebo.ab.
22. drug therapy.fs.
23. randomly.ab.
24. trial.ti.
25. groups.ab.
26. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. (animals not (humans and animals)).sh.
28. 26 not 27
29. 17 and 28

Appendix 2. Draft 'summary of findings' table

Interventions to improve insulin resistance for the prevention of endometrial cancer

Patient or population: women over the age of 18 without pre-existing endometrial cancer or atypical hyperplasia, women with insulin resistance.

Settings: in- and out-patient

Interventions: Interventions designed to improve insulin resistance

Comparison: other interventions to improve insulin resistance, usual care or placebo

Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)	Comment
	Assumed risk	Corresponding risk				
Incidence of endometrial cancer or atypical hyperplasia, or both						
Regression of histological atypia or cancer						
Improvement in measures of insulin resistance						

Interventions to improve insulin resistance for the prevention of endometrial cancer (Protocol)

(Continued)

Weight loss

Physical activity

Change in measures of endometrial proliferation

Frequency of adverse events

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE: Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are uncertain about the estimate.

WHAT'S NEW

Date	Event	Description
17 January 2020	Amended	Update to author affiliation.

CONTRIBUTIONS OF AUTHORS

All authors have contributed to the study conception and design.

Acquisition of data will be undertaken by Vanitha Sivalingam, Sarah Kitson and Michelle MacKintosh.

Analysis and interpretation will be undertaken by Vanitha Sivalingam, Sarah Kitson, Michelle MacKintosh, Martin Rutter and Emma Crosbie

Drafting of manuscript will be performed by Vanitha Sivalingam, Sarah Kitson and Emma Crosbie and will be reviewed by all authors.

The review update will be undertaken by Emma Crosbie.

DECLARATIONS OF INTEREST

Vanitha Sivalingam: None known

Sarah Kitson: None known

Michelle MacKintosh: None known

Martin Rutter: None known

Emma Crosbie: None known