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Metformin for endometrial hyperplasia (Protocol)

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[Intervention Protocol]

Metformin for endometrial hyperplasia

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine the efficacy and safety of metformin in treating women with endometrial hyperplasia.

BACKGROUND

Description of the condition

Endometrial hyperplasia is a precancerous endometrial lesion that commonly presents with abnormal uterine bleeding. It is thought to be due to unopposed, prolonged exposure of the endometrium to oestrogen and, if managed expectantly, can progress to endometrial carcinoma, although the condition may resolve spontaneously. It is diagnosed histologically and can be subsequently categorised into four subtypes; simple, simple with atypia, complex and complex with atypia (Kurman 1985). Risk of progression to endometrial carcinoma is dependent on the type of endometrial hyperplasia, and progression rates vary widely across the literature. This discrepancy is likely due, in part, to the fact that many cases of endometrial hyperplasia, especially when atypia is present, are managed pre-emptively with a hysterectomy. However, atypia is thought to be a strong risk factor for progression to adenocarcinoma (Kurman 1985). Progression rates have been reported as less than 5% for non-atypical hyperplasia but 28% for atypical hyperplasia cumulatively over 20 years. This difference in progression risk has also been seen at interval-specific time points of four years, nine years and 20 years post diagnosis (Lacey 2010). Risk factors for endometrial hyperplasia are, predictably, very similar to those for endometrial carcinoma and include obesity, diabetes mellitus, nulliparity, tamoxifen use, oestrogen therapy and polycystic ovarian syndrome (PCOS) (Torres 2012).

Polycystic ovarian syndrome is a metabolically driven gynaecological disorder thought to affect 10% of women of child-bearing age (Chang 2002). A diagnosis of PCOS must fulfil the widely accepted Rotterdam criteria of two or more of the following in the absence of another cause of chronic anovulation: hyperandrogenism (clinical or biochemical), chronic oligo/anovulation and polycystic ovaries apparent on ultrasound (ESHRE/ASRM 2004). Prevalence of endometrial hyperplasia in women with PCOS varies greatly in the literature - between 1% and 48.8% (Cheung 2001; Holm 2012; Rudnicka 2009; Tingthanatikul 2006) - but risk of endometrial carcinoma is well founded, as women with PCOS

possess a three-fold increased risk of developing endometrial carcinoma when compared with the non-PCOS population (Haoula 2012).

The aim of endometrial hyperplasia treatment, whether or not PCOS is a co-morbidity, is to control abnormal vaginal bleeding while minimising risk of progression to endometrial carcinoma. Historically, endometrial hyperplasia without atypia has been medically treated with oral progestogens (alone or in combination with oestrogen in PCOS) or intrauterine progestogens, inhibiting oestrogen-driven cell growth and inducing withdrawal bleeds (Yang 2011). This treatment provides the benefit of preserving fertility but is associated with side effects - in the short term, headaches, mood changes, acne or breast tenderness, and over the longer term, risk of a thromboembolic event or breast cancer. These longer-term side effects can be mitigated by educating women on the symptoms of thromboembolic events and by ensuring that they attend regular breast cancer screening programmes. This approach has the effect of potentially hindering compliance, consequently producing a relatively high relapse rate. In one study, 30.3% and 13.7% of women treated with oral progestogens and intrauterine levonorgestrel, respectively, had relapse of their endometrial hyperplasia (Gallos 2013). In women with atypia and in those who are resistant to progestogens, surgical hysterectomy is the treatment of choice.

Description of the intervention

Metformin, a biguanide that acts as an insulin sensitiser, is the most commonly used oral hypoglycaemic agent in type 2 diabetes mellitus. It acts to inhibit hepatic gluconeogenesis, decreasing liver glucose production and thereby decreasing levels of circulating glucose and insulin.

Metformin is also prescribed for women with PCOS to induce weight loss and improve menstrual regularity, both as monotherapy and in combination with a progestogen. It is frequently used to treat ovulation dysfunction in women with PCOS when they have shown resistance to treatment with clomiphene. Despite widespread use of metformin in women with PCOS, no definitive improvement in clinical or biochemical features has been shown on systematic review when metformin is compared with the oral contraceptive pill (Costello 2007). It has an established side effect profile, including nausea and vomiting, diarrhoea, abdominal pain and changes in taste, as well as rarer or less publicised effects including lactic acidosis or decreased B12 absorption, possibly leading to anaemia and potentially irreversible neuronal damage if left unmonitored and uncorrected for prolonged periods (de Jager 2010).

How the intervention might work

Hyperinsulinaemia secondary to insulin resistance is thought to exhibit a mitogenic effect, inducing cell division via mitosis - a risk factor for hyperplasia - and, ultimately, carcinoma development. This effect is likely due to its activity at the insulin-like growth factor-1 receptor, promoting proliferation and angiogenesis, which can be demonstrated by the positive correlation between diabetes and breast and gynaecological cancers (Vrachnis 2016). Insulin-mediating effects of metformin, then, show evidence of reducing incidence and improving survival among these malignancies, although the evidence is mixed (Chlebowski 2012; Nevadunsky 2014). The link between insulin resistance and cell proliferation offers an intriguing potential therapeutic target to reverse hyperplasia and prevent endometrial carcinoma. Some early trials have corroborated this link, showing efficacy of metformin in inducing endometrial atrophy in benign endometrial proliferative disorders; one reported atrophy and therefore reversal of endometrial hyperplasia in 96% of women treated with metformin (Tabrizi 2014).

Other proposed mechanisms of the anti-cancer properties of metformin include its direct effects on cell signalling pathways, including inhibition of the mammalian target of rapamycin (mTOR) and inhibition of mitogen-activated protein kinase (MAPK) and Akt activity. These pathways are involved in cell proliferation and therefore play a key role in both hyperplasia and cancerous lesions in any tissue. As metformin inhibits these pathways, cell proliferation will be hindered, reducing the chance of development of cancerous lesions (Alimova 2009; Ben 2011).

Why it is important to do this review

Current medical therapy for endometrial hyperplasia involves multiple side effects and leaves the risk of recurrence. Therefore, a systematic review of a novel, alternative therapy is needed to collate the evidence to date and guide future human trials. Risk of progression from endometrial hyperplasia to carcinoma is significant; up to 40% of women suffering from endometrial hyperplasia with atypia go on to develop carcinoma, the most common fatal gynaecological malignancy (Kim 2013). This rate is expected to increase by up to 100% globally over the next 20 years (Dowling 2011). The biguanide insulin sensitiser metformin has been linked to reversal of endometrial hyperplasia (Tabrizi 2014) and, if it can be used in this way, may contribute to decreasing the prevalence of endometrial carcinoma without leading to the fertility consequences of current therapies. Metformin is also used as an alternative therapy in women with PCOS, among whom risk of endometrial hyperplasia is increased. However, the mode of action, efficacy and safety of metformin remain unclear. This review may help to clarify its role in the treatment of women with this disease.

OBJECTIVES

To determine the efficacy and safety of metformin in treating women with endometrial hyperplasia.

METHODS

Criteria for considering studies for this review

Types of studies

The review will consider only randomised controlled trials (RCTs), both published and unpublished, as eligible for inclusion. We will include cross-over trials, but we will use in the analysis only data from the first phase, as cross-over is not a valid study design for the purposes of this review.

Types of participants

We will select women who have histologically confirmed endometrial hyperplasia of any type as the study population of the review.

Types of interventions

We will include trials of metformin compared with placebo or no treatment, conventional medical treatment (typically progestogens, e.g. oral or intrauterine) or any other active intervention. We will include trials that provide co-interventions (e.g. metformin plus progesterone vs progesterone) but will analyse these studies separately.

Types of outcome measures

Primary outcomes

- Regression of endometrial hyperplasia histology (with or without atypia) towards normal histology.

Secondary outcomes

- Recurrence of endometrial hyperplasia.
- Progression of endometrial hyperplasia to endometrial cancer.
- Hysterectomy rate.
- Abnormal uterine bleeding.
- Health-related quality of life, as reported in the included study.
- Adverse effects during treatment, as reported in the included study.

We will report outcomes measured after short-term treatment (up to six months post treatment), medium-term treatment (six to 12 months post treatment) and long-term treatment (more than 12 months post treatment).

Search methods for identification of studies

We will search for all published and unpublished RCTs of metformin for endometrial hyperplasia without language restriction. Review authors will liaise with the Cochrane Gynacology and Fertility Group Trials Search Co-ordinator when conducting the search.

Electronic searches

In accordance with guidance from the Cochrane Gynacology and Fertility Group, we will create search strategies for the following electronic databases to identify all relevant RCTs.

- Cochrane Gynaecology and Fertility Specialised Register (inception to present) (Appendix 1).
- Cochrane Central Register of Controlled Trials (Ovid CENTRAL) (inception to present) (Appendix 2).
- Ovid MEDLINE (inception to present) (Appendix 3).
- Ovid EMBASE (inception to present) (Appendix 4).
- EBSCO Cumulative Index to Nursing and Allied Health Literaure (CINAHL) (inception to present) (Appendix 5).
- PubMed (inception to present) (Appendix 6).
- Google Scholar (inception to present) (Appendix 7).

We will perform a further search to identify ongoing or unpublished trials related to the review.

- ClinicalTrials.gov (inception to present) (Appendix 8).
- World Health Organization International Trials Registry Platform search portal (inception to present) (Appendix 9).
- OpenGrey (inception to present) (Appendix 10).
- Latin American Caribbean Health Sciences Literature (LILACS) (inception to present) (Appendix 11).

We will present a list of search strings in the appendices and will email the contact persons of all unpublished trials identified to assess these studies for potential inclusion.

Searching other resources

To identify additional trials, we will handsearch the bibliographies of all included studies, as well as any reviews on the topic. We will also handsearch the European Society of Human Reproduction and Embryology (ESHRE) 2015 and the American Society for Reproductive Medicine (ASRM) 2015 conference abstracts for relevant presentations. Previous abstracts from these conferences are already incorporated into the Cochrane Gynaecology and Fertility Specialised Register.

Data collection and analysis

Selection of studies

We will add to a reference manager (Covidence) the titles and abstracts of all studies retrieved by electronic searches and will remove duplicates. Two review authors (NC, TO, JS, HS) will independently review each entry and will assess titles and abstracts for potential inclusion in the review. We will seek full-text reports for potentially relevant studies. Again, two review authors (NC, TO, JS, HS) will independently assess each full-text report against the inclusion criteria and will document a justification for rejection of each study. Review authors will resolve disagreements between them regarding trial suitability by discussion or by consultation with a third review author. We will screen studies for duplicate publication by comparing study author names, locations, dates and durations. When uncertainty about study methods or the possibility of duplicate studies arises, we will contact the authors of relevant papers.

We will construct a flow chart to illustrate selection of studies for inclusion in this review according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher 2009).

Data extraction and management

Two review authors will independently extract data using a data extraction form that is based on the 'Checklist of items to consider in data collection or data extraction' provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). During study selection, if we find a study that has been published multiple times, we will extract and collate the data into a single file. We will treat such studies as a single unit of interest for the review and will attribute multiple references to the single file.

When necessary, we will liaise with study authors to obtain additional data on their methods and/or results.

Assessment of risk of bias in included studies

Two review authors (from NC, TO, HS or JS) will independently assess each included study for risk of bias by using the Cochrane 'Risk of bias' assessment tool, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will categorise bias in the following manner.

- Selection bias (random sequence generation and allocation concealment).
- Performance bias (blinding of participants and personnel).
- Detection bias (blinding of outcome assessments).
- Attrition bias (incomplete outcome data).
- Reporting bias (selective reporting).
- Other bias (other sources of bias).

We will classify risk of bias as 'low', 'high' or 'unclear' for all domains mentioned above by using the 'Criteria for judging risk of bias' in the 'Risk of bias' assessment tool (Higgins 2011). We will resolve disagreements by discussion and when necessary by consultation with a third review author. We will fully justify judgements made and will include this information in the 'Risk of bias' table. We will account for findings of this assessment when we interpret findings of the review, as when performing the sensitivity analysis. We will report the level of risk chosen and evidence used to make that judgement, for example, quotes from the text, in a 'Characteristics of included studies' table. To minimise bias in selective reporting of trial outcomes, when possible, we will compare published protocols versus methods described in the final study.

Measures of treatment effect

For dichotomous data (e.g. regression of endometrial hyperplasia, progression to endometrial carcinoma), we will calculate the Mantel-Haenszel odds ratio (OR) from the numbers of events in control and intervention groups.

For continuous data, we will use means, standard deviations and mean differences (MDs). We will treat ordinal data, such as side effect severity scoring systems or health-related quality of life questionnaires, as continuous data for purposes of analysis. When different scales are used to report similar outcomes (e.g. change in endometrial thickness), we will calculate the standardised mean difference (SMD). We will express the SMD effect as small (0.2 to < 0.5), medium (0.5 to < 0.8) or large ($\geq$ 0.8).

We will provide 95% confidence intervals (CIs) for all outcomes. When ORs and MDs cannot be derived from the data, we will perform an alternative statistical analysis of included studies when possible. We will report the values produced by analysis in full, along with the direction and magnitude of effect of the intervention, and whether or not findings are statistically significant.

Unit of analysis issues

We will perform the primary analysis per woman. When a valid analysis is not possible (e.g. 'per cycle' data), we will briefly summarise the data but will not include them in the meta-analysis. We will include in the analysis only first-phase data from cross-over trials.

Dealing with missing data

We will analyse only available data. When contacting study authors for missing information, we will send a first reminder email 14 days and a second reminder email 21 days after the initial email. Should we determine that data are missing, we will address the potential impact of this fact in the Discussion section of the review.

Assessment of heterogeneity

We will consider whether clinical and methodological characteristics of included studies are sufficiently similar for meta-analysis to provide a clinically meaningful summary. We will assess statistical heterogeneity by using the measure of I^2. We will consider I^2 greater than 50% to indicate substantial heterogeneity (Higgins 2003; Higgins 2011).

Assessment of reporting biases

Reporting bias is a potential issue for all reviews. We will aim to identify and minimise reporting bias in our analysis by creating a comprehensive search strategy and utilising a multitude of electronic databases, including those that record unpublished work and work prepared in languages other than English. This should ensure that we maximise the yield of eligible studies included in the review and identify cases of data duplication.

If we include 10 or more studies in a single analysis, we will use a funnel plot to explore the possibility of small-study effects (i.e. the tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

If identified studies are sufficiently similar, we will combine the data using a fixed-effect model for the following comparisons.

- Metformin versus placebo or no treatment.
- Metformin versus progestogens.
- Metformin versus other active intervention.
- Metformin plus co-intervention versus co-intervention alone.

We will stratify analyses by dose of metformin (high, moderate, low).

We will graphically display results of these meta-analyses, with increasing odds (regardless of whether the outcome is beneficial) demonstrated by a marker right of the centre-line and decreasing odds by a marker left of the centre-line.

Subgroup analysis and investigation of heterogeneity

When data are available, we will conduct subgroup analyses to determine separate evidence within the following subgroups.

- Women with PCOS.
- Women with atypical endometrial hyperplasia.

Should pooled data demonstrate substantial heterogeneity (> 50%), we will consider additional subgroup analyses (e.g. by dose or route of metformin) and/or sensitivity analyses. We will acknowledge the degree of heterogeneity when interpreting the meta-analysis.

Sensitivity analysis

We will conduct a sensitivity analysis for the primary outcome to determine whether the conclusions are robust to our choice of methods with regards to study eligibility and analysis. Through this sensitivity analysis, we will explore whether the review conclusions would have been different if:

- all studies with high risk of bias in one or more domains were excluded from the analysis;
- a random-effects model had been implemented; or
- the effect estimate had been expressed as risk ratio (RR) rather than OR.

Overall quality of the body of evidence: Summary of findings table

We will prepare a 'Summary of findings' table by using GRADEpro Guideline Development Tool software. In this table, we will present a concise overview of the quality of available evidence pertaining to the review outcomes (regression of endometrial hyperplasia towards normal histology, recurrence of endometrial hyperplasia, progression of endometrial hyperplasia to endometrial cancer, hysterectomy rate, abnormal uterine bleeding, health-related quality of life, as reported in included studies and adverse effects during treatment as reported in included studies). In accordance with GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) criteria (study limitations, consistency of effect, imprecision, indirectness and publication bias), we will rate the quality of the evidence as 'high', 'moderate', 'low' or 'very low'. We will document the justification for each grade awarded and will incorporate the overall grade into the final conclusion drawn from the results.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Gynaecology and Fertility Specialised Register search strategy

Keywords CONTAINS “endometrial hyperplasia” or “endometrial proliferation” or “endometrial thickness” or “proliferation” or “hyperplasia” or Title CONTAINS “endometrial hyperplasia” or “endometrial proliferation” or “endometrial thickness” or “proliferation” or “hyperplasia”
AND
Keywords CONTAINS “metformin” or “glucophage” or Title CONTAINS “metformin” or “glucophage”

Appendix 2. CENTRAL search strategy

1. exp Endometrial Hyperplasia/
2. (endometri$ adj5 hyperplas$).tw.
3. (endometri$ adj3 proliferat$).tw.
4. or/1-3
5. exp Metformin/
6. metformin.tw.
7. glucophage.tw.
8. (dimethylbiguanidine or dimethylguanylguanidine).tw.
9. (dimethylbiguanidium or glucovance).tw.
10. or/5-9
11. 4 and 10

Appendix 3. MEDLINE search strategy

1. exp Endometrial Hyperplasia/
2. (endometri$ adj5 hyperplas$).tw.
3. (endometri$ adj3 proliferat$).tw.
4. or/1-3
5. exp Metformin/
6. metformin.tw.
7. glucophage.tw.
8. (dimethylbiguanidine or dimethylguanylguanidine).tw.
9. (dimethylbiguanidium or glucovance).tw.
10. or/5-9
11. 4 and 10
12. randomized controlled trial.pt.
13. controlled clinical trial.pt.
14. randomized.ab.
15. randomised.ab.
16. placebo.tw.
17. clinical trials as topic.sh.
18. randomly.ab.
19. trial.ti.
20. (crossover or cross-over or cross over).tw.
21. or/12-20
22. exp animals/ not humans.sh.
23. 21 not 22
24. 11 and 23

Appendix 4. EMBASE search strategy

1. exp endometrium hyperplasia/
2. (endometri$ adj5 hyperplas$).tw.
3. (endometri$ adj3 proliferat$).tw.
4. or/1-3
5. exp metformin/
6. metformin.tw.
7. glucophage.tw.
8. (dimethylbiguanidine or dimethylguanylguanidine).tw.
9. (dimethylbiguanidium or glucovance).tw.
10. or/5-9
11. 4 and 10
12. Clinical Trial/
13. Randomized Controlled Trial/
14. exp randomization/
15. Single Blind Procedure/
16. Double Blind Procedure/
17. Crossover Procedure/
18. Placebo/
19. Randomi?ed controlled trial$.tw.
20. Rct.tw.
21. random allocation.tw.
22. randomly.tw.
23. randomly allocated.tw.
24. allocated randomly.tw.

25. (allocated adj2 random).tw.
26. Single blind$.tw.
27. Double blind$.tw.
28. ((treble or triple) adj blind$).tw.
29. placebo$.tw.
30. prospective study/
31. or/12-30
32. case study/
33. case report.tw.
34. abstract report/ or letter/
35. or/32-34
36. 31 not 35
37. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
38. 36 not 37
39. 11 and 38

Appendix 5. CINAHL search strategy

1. (MM "Endometrial Diseases+")
2. TX (endometr* N5 hyperplas*)
3. TX (endometr* N3 proliferat*)
4. 1 OR 2 OR 3
5. (MM "Metformin")
6. TX Metformin
7. TX glucophage
8. TX (dimethylbiguanidium or glucovance)
9. 5 OR 6 OR 7 OR 8
10. 4 AND 9

Appendix 6. PubMed search strategy

1. Endometrial Hyperplasia[mh]
2. (endometri* and hyperplas*)[tw]
3. (endometri* and proliferat*)[tw]
4. or/1-3
5. Metformin[mh]
6. metformin[tw]
7. glucophage[tw]
8. (dimethylbiguanidine or dimethylguanylguanidine)[tw]
9. (dimethylbiguanidium or glucovance)[tw]
10. or/5-9
11. 4 and 10
12. randomized controlled trial[ptyp]
13. controlled clinical trial[ptyp]
14. randomized[tw]
15. randomized[tw]
16. placebo[tw]
17. randomly[tw]
18. trial[tw]
19. (crossover or cross-over or cross over)[tw]
20. or/12-20
21. animals[mh] not humans[mh]

22. 20 not 21
23. 11 and 22

Appendix 7. Google Scholar search strategy

Keywords include: “endometrium”, “endometrial”, “hyperplasia, ”proliferation“, ”metformin“

Appendix 8. ClinicalTrials.gov search strategy

(endometrial OR endometrium) AND (hyperplasia OR proliferation) AND (metformin OR glucophage OR dimethylbiguanidine OR dimethylguanylguanidine OR glucovance OR dimethylbiguanidium)

Appendix 9. World Health Organization International Trials Registry Platform search strategy

(endometrial OR endometrium) AND (hyperplasia OR proliferation) AND (metformin OR glucophage OR dimethylbiguanidine OR dimethylguanylguanidine OR glucovance OR dimethylbiguanidium)

Appendix 10. OpenGrey search strategy

(endometrial OR endometrium) AND (hyperplasia OR proliferation) AND (metformin OR glucophage OR dimethylbiguanidine OR dimethylguanylguanidine OR glucovance OR dimethylbiguanidium)

Appendix 11. LILACS search strategy

(endometrial OR endometrium) AND (hyperplasia OR proliferation) AND (metformin OR glucophage OR dimethylbiguanidine OR dimethylguanylguanidine OR glucovance OR dimethylbiguanidium)

CONTRIBUTIONS OF AUTHORS

WA and NC initiated the review; NC, TO and HS drafted and finalised the background and objectives; JS, TO and HS drafted and finalised the methods sections with assistance from CM. WA reviewed the final protocol.

DECLARATIONS OF INTEREST

WA is a Clinical Associate Professor and a Consultant Gynaecologist at Queen’s Medical Centre, at Nottingham, in the UK. He previously submitted an application to the Nottingham Clinical Trials Unit (in the process of developing a research grant application to the UK NIHR) to conduct a clinical trial comparing metformin with Provera for treatment of endometrial hyperplasia. This research grant application was unsuccessful because of the impression that a Cochrane review was necessary to support the trial.

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