Metformin as an Adjunct to Progestin Therapy in Endometrial Hyperplasia and Early-Stage Endometrial Cancer: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Patricia Ann A. Factor, MD[1] and Koleen C. Pasamba, MD[2]

[1]*Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Philippine General Hospital, University of the Philippines Manila*
[2]*Department of Obstetrics and Gynecology, Philippine General Hospital, University of the Philippines Manila*

ABSTRACT

Background and Objective. Metformin has been studied for its anti-proliferative effects on endometrial cells, and it is hypothesized to have a synergistic effect with progestin therapy in suppressing endometrial cell proliferation. This systematic review and meta-analysis aimed to determine the efficacy of adjunctive metformin in the clinical regression of endometrial hyperplasia and early-stage endometrial carcinoma. There have been previous systematic reviews that investigated the role of metformin with progesterone for endometrial hyperplasia and endometrial cancer, but they have included retrospective cohorts, and are thus have higher risk of bias.

Methods. This meta-analysis followed the Cochrane methodology and adhered to the PRISMA 2020 guidelines. Randomized controlled trials (RCTs) were included if they enrolled reproductive-aged women with endometrial hyperplasia (with and without atypia) and endometrial carcinoma who were treated with progestin and metformin. The primary outcome was the complete response rate at 12-16 weeks, and secondary outcomes included relapse rate, clinical pregnancy rate, and live birth rate. Subgroup analysis of endometrial hyperplasia without atypia vs hyperplasia with atypia and early endometrial cancer was also included. Odds ratios (ORs) and 95% confidence intervals (CIs) were used for dichotomous data.

Results. Six RCTs were included. The addition of metformin to progestin therapy may increase the complete response rate of endometrial hyperplasia without atypia (OR 5.12, 95% CI 1.17 to 22.41; n = 102) and live birth rates (OR 2.51, 95% CI 1.34 to 4.69; n = 188) compared to progestin therapy alone, but the certainty of the evidence is low. Metformin did not have a significant effect on the clinical response of endometrial hyperplasia with atypia and endometrial carcinoma, relapse rates, and clinical pregnancy rates.

Conclusion. Current evidence is uncertain on the potential benefit of metformin with progestin in endometrial hyperplasia and carcinoma. Future high-quality randomized controlled trials with larger sample sizes and longer follow-up periods are needed to support practice recommendations.

Keywords: endometrial hyperplasia, endometrial cancer, metformin, progesterone

Paper presentation – International Gynecologic Cancer Society Annual Convention, November 5-7, 2023, Seoul, Korea.

eISSN 2094-9278 (Online)
Published: June 28, 2024
https://doi.org/10.47895/ amp.v58i11.8155

Corresponding author: Patricia Ann A. Factor, MD
Division of Reproductive Endocrinology and Infertility
Department of Obstetrics and Gynecology
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Ermita, Manila 1000, Philippines
Email: pafactor@up.edu.ph
ORCiD: https://orcid.org/0000-0001-8081-6242

INTRODUCTION

In 2020, endometrial cancer ranked as the sixth most commonly diagnosed cancer in women, with 417,000 new cases diagnosed.[1] Although most cases are diagnosed in the postmenopausal period, there has been an increasing incidence of endometrial cancer in women younger than 40 years old.[2]

Studies indicate that endometrial cancer incidence rates have increased over time and in successive generations, particularly in countries with socioeconomic movement, such as Japan, Singapore, India, and the Philippines. These increases are hypothesized to reflect the rise in prevalence factors such as obesity and physical inactivity in younger generations.[3]

Endometrial hyperplasia is a precursor lesion to endometrial adenocarcinoma and is characterized by uncontrolled proliferation and mutations in the endometrial glands, induced by unopposed estrogen. Medical therapy with progestins is the standard of treatment in young women who are still desirous of pregnancy.[4] Due to the rising incidence of endometrial hyperplasia and endometrial cancer in younger women, preserving fertility is a critical aspect of treatment. Various therapies have been explored to improve outcomes in this population.[5]

A previous systematic review analyzed observational studies and demonstrated that the use of metformin in combination with progesterone reduced the relapse rates of atypical endometrial hyperplasia and endometrial cancer. However, no effect was observed on remission rates and pregnancy outcomes.[6] This study is limited by its observational nature and high risk of bias.

Subsequent to this review, several randomized controlled trials have been conducted to investigate the effect of adjunctive metformin on remission, relapse, and pregnancy outcomes.[7–11] These trials provide a more rigorous evaluation of the potential benefits of metformin therapy.

Obesity, insulin resistance, and hyperinsulinemia are significant risk factors for endometrial cancer, as they increase the levels of insulin and insulin-like growth factor-1 (IGF-1), which stimulate the proliferation of endometrial cells. Metformin, a biguanide antidiabetic agent, decreases insulin and IGF-1 levels and increases progesterone receptor concentration and sensitivity, suggesting that it may have anti-proliferative effects on endometrial cells.[5] Adjunctive metformin might have a synergistic effect with progestin therapy in suppressing endometrial cell proliferation.[6]

As the incidence of endometrial hyperplasia and endometrial carcinoma in young women increases, it is crucial to explore therapeutic options that can improve outcomes while preserving fertility. Progestin therapy remains the standard of care for patients who desire future pregnancy, but the addition of metformin to progestin therapy may enhance the clinical response and improve pregnancy outcomes.

The aim of this review is to determine if the addition of metformin to progestin in young women with endometrial hyperplasia and carcinoma is effective in improving clinical response and pregnancy outcomes. The specific objectives are: 1) to determine if adjunctive metformin increases clearance rate of both hyperplasia without atypia and early endometrial cancer and hyperplasia with atypia; 2) to assess whether adding metformin as a supplementary treatment reduces the recurrence rates of endometrial hyperplasia and endometrial cancer; and 3) to evaluate the impact of adjunctive metformin on clinical pregnancy rate and live birth rates in patients with endometrial hyperplasia and endometrial cancer still desirous of pregnancy.

METHODS

This protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) on April 21, 2023 (CRD42023415911). Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID = CRD42023415911

Keywords used in the literature search are as follows: Metformin [MeSH Terms] OR metformin, endometrial neoplasm [MeSH Terms] OR endometrial hyperplasia OR endometrial cancer OR endometrial hyperplasia, and progestins [MeSH Terms] OR medroxyprogesterone acetate OR megestrol acetate OR levonorgestrel IUD OR progesterone.

All published and unpublished randomized controlled trials that investigated the impact of combined metformin and progesterone treatment on clearance rate, recurrence rate, and pregnancy outcomes in patients with endometrial hyperplasia (with and without atypia) and early-stage endometrial cancer were included. Excluded from this analysis were case reports, observational studies, and non-randomized trials.

We included trials that recruited reproductive-aged women with a histologically confirmed diagnosis of endometrial hyperplasia and early-stage endometrial cancer. Patients presenting with advanced disease were excluded from the study.

The intervention investigated was metformin given in combination with progestins for the purpose of fertility-sparing treatment of endometrial hyperplasia and early-stage endometrial cancer. Studies that gave metformin alone will be excluded. We included all forms of progesterone (medroxyprogesterone acetate, megestrol acetate, and levonorgestrel intrauterine device).

The primary efficacy outcome was clearance rate at 12-16 weeks and relapse rate. Secondary outcomes included clinical pregnancy rate and live birth rate.

We searched the following databases from inception until April 30, 2023: *The Cochrane Library*, PubMed, Scopus, *Google Scholar*, *MedRXIV*, and *Research Square*.

We also searched databases of unpublished, planned and ongoing trials including the EU Clinical Trials register (https://www.clinicaltrialsregister.eu/), ClinicalTrials.gov (http://clinicaltrials.gov/), and the World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal (https://trialsearch.who.int/).

Data Collection and Analysis

Two review authors (PF, KP) independently scanned the abstract, title, or both, of every record retrieved, to determine which studies should be assessed further. All potentially relevant articles were retrieved as full text articles

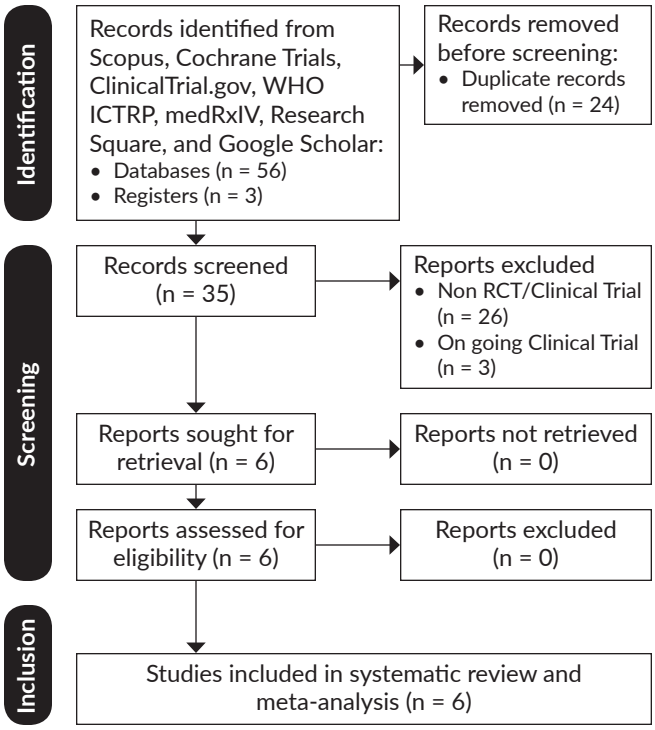

Figure 1. Study flow diagram.

and reviewed independently. The selection process adhered to the guidelines specified in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart, which was adapted for this study (Figure 1).

Data Extraction and Management

Data was extracted by the two review authors (PF, KP). Any disagreements were resolved by discussion. All data was encoded in Review Manager (RevMan v 5.4.1).

Assessment of Risk of Bias in Included Studies

Two review authors (PF, KP) independently assessed the risk of bias of each included study. Disagreements were resolved by discussion. We used the Cochrane Collaboration's tool for assessment of risk of bias.

'Risk of bias criteria' was judged as 'low risk', 'high risk' or 'unclear risk'. Individual bias items were evaluated as described in the *Cochrane Handbook for Systematic Reviews of Interventions*. The risk of bias within and across studies were presented graphically (Figures 2 and 3).

Measures of treatment Effect

Dichotomous data was expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

Assessment of Heterogeneity

The presence of heterogeneity in the data was determined through both visual inspection of the forest plot and the utilization of a standard Chi-square test, with a significance level of $\alpha = 0.05$. The I^2 statistic was employed to evaluate the impact of heterogeneity on the meta-analysis, with a value of 50% or higher signifying a significant level of inconsistency.

Data Synthesis

Because of substantial clinical and methodological heterogeneity, data for complete response at 12-16 weeks and clinical pregnancy rates was summarized by means of a random-effects model.

Subgroup Analysis and Investigation of Heterogeneity

The authors did a subgroup analysis of endometrial hyperplasia (without atypia) vs atypical endometrial hyperplasia and early-stage endometrial cancer for the remission rates.

RESULTS

Search Strategy

We identified 59 reports, twenty-four were duplicates. Twenty-nine were screened out at title and abstract stage. Six studies were assessed for eligibility and were included in the analysis. The study selection schematic diagram is shown in Figure 1.

Study Characteristics

We included six randomized controlled trials, all are published studies: Shan 2014, Yang 2020, Ravi 2021, Tehranina 2021, Janda 2021, and Yuan 2022.[7–12] The baseline characteristics of the included studies are summarized in Table 1.

Risk of Bias in Included Studies (Figures 2 and 3)

Effects of interventions

Primary Outcomes

Clearance rate at 12-16 weeks

In patients who are being treated with progestins for endometrial hyperplasia and endometrial carcinoma, the initial biopsy to assess treatment response is done after 12-16 weeks of treatment. Looking at the pooled effects, adjunctive metformin seems to be associated with increased clearance rates at 12-16 weeks (OR 1.85, 95% CI 1.13, 3.03; n = 441) when compared to progesterone monotherapy alone.

A subgroup analysis was done to assess if there was a difference in the effect of adjunctive metformin on endometrial hyperplasia (without atypia) vs atypical endometrial hyperplasia and early-stage endometrial cancer. For atypical hyperplasia and early-stage endometrial cancer, the odds ratio is 1.63 with 95% CI (0.98, 2.72; n = 339); with the confidence interval crossing the line of no benefit, the evidence is uncertain about the benefit of adjunctive metformin on the

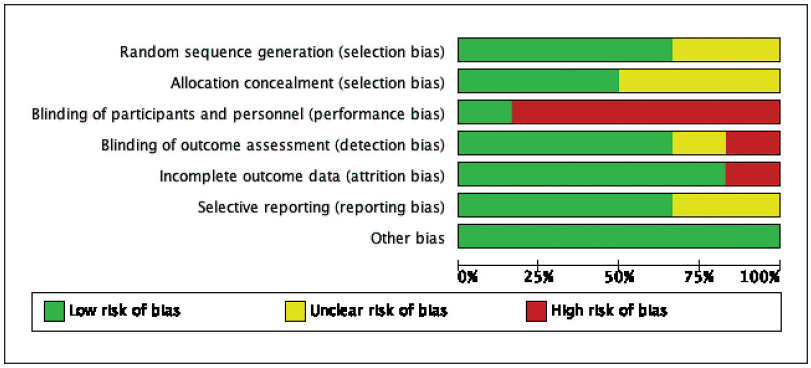

Figure 2. ***Risk of bias graph:*** Review author's judgment about each risk of bias item presented as a percentage across all included studies.

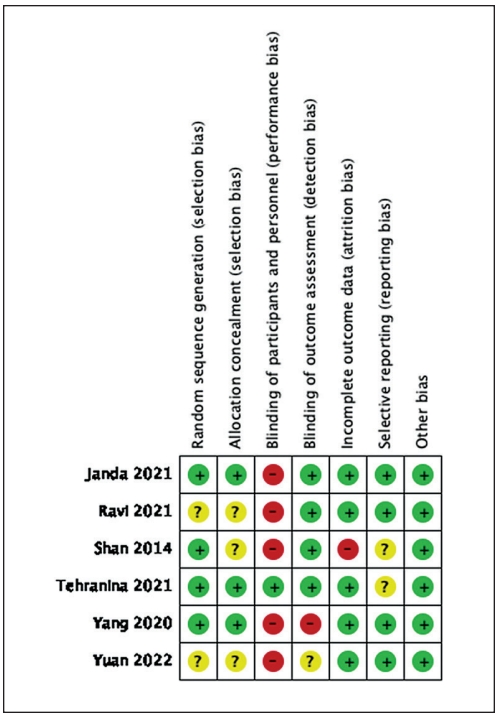

Figure 3. ***Risk of bias summary:*** Review authors' judgments about each risk of bias item for each included study.

Table 1. Characteristics of Included Studies

References	Country and time of realization	Participants and main inclusion criteria	Intervention and timing	Intervention group	Control group	Outcomes
Shan et al., 2014	China Obstetrics and Gynecology Hospital of Fudan University August 2012 and January 2013	Patients who were diagnosed with **endometrial atypical hyperplasia** (aged ≤45 years), had a desire for preservation of fertility, and met at least one metabolic syndrome (MS) criterion were enrolled	MA group received 160 mg of MA daily, MET group received the 160 mg MA plus 0.5 g of metformin thrice daily	MA + Metformin = 8 Age 34 ± 7.1	MA alone = 8 Age 36.4 ± 4.2	Complete response after 12 weeks of treatment
Yang et al., 2020	China Obstetrics and Gynaecology Hospital of Fudan University, Shanghai, China October 2013 to October 2017	18–45 years old, pathologically diagnosed with **atypical endometrial hyperplasia or endometrial carcinoma**; desire to preserve their fertility; no signs of suspicious myometrial invasion or extrauterine; no contraindication for metformin, MA or pregnancy; no hormone or metformin treatment within 6 months before entering the trial; not pregnant when participating in the trial	Megestrol acetate (MA)-only group received continuous MA (160 mg orally, daily), metformin plus MA group received continuous MA (160 mg orally, daily) plus metformin (500 mg orally, three times a day)	MA + Metformin N = 74 Age 33.4 ± 5.2 BMI 24.6 ± 4.1 Histology AEH 62 (83.8) EEC 12 (16.2)	MA alone N = 74 Age 32.0 ± 4.5 BMI 24.7 ± 5.2 Histology AEH 61 (80.3) 15 (19.7)	1. Complete response rate at 16 weeks (and 32 weeks) 2. Relapse rate 3. Pregnancy 4. Live birth 5. Adverse events

Table 1. Characteristics of Included Studies *(continued)*

References	Country and time of realization	Participants and main inclusion criteria	Intervention and timing	Intervention group	Control group	Outcomes
Ravi et al., 2021	India Department of Obstetrics and Gynaecology and the Department of Pathology, Post Graduate Institute of Medical Education and Research, Chandigarh, India July 2016 to June 2018	presented with AUB and had a histopathological diagnosis of **endometrial hyperplasia without atypia**	LNG-IUS (MIRENA) 52 mg Levonorgestrel with a release rate of approximately 20 µg per day LNG-IUS + 500 mg metformin once a day for 1 week followed by 500 mg metformin twice a day for the rest of the duration of the study in addition to LNG-IUS	LNG-IUS + Metformin N = 25 Age 44.2 ± 5.82 BMI 29.75 ± 6.85	LNG-IUS alone N = 26 Age 44.73 ± 5.96 BMI 26.74 ± 3.70	Complete response at 6 months
Tehranian et al., 2021	Iran Arash women's hospital affiliated to Tehran University of Medical Sciences, Tehran, Iran January 2016 to September 2018	women aged 18–75 years with **endometrial hyperplasia without atypia**	40 mg megestrol acetate for 14 days of one month and 1000 mg metformin daily 40 mg megestrol acetate for 14 days of one month and 2 placebo pills	MA + metformin N = 30 Age 44.85 ± 6.80 BMI 18.51 ± 0.72	MA + placebo N = 30 Age 43.16 ± 6.08 BMI 28.6 ± 0.97	Regression rate after 3 months of treatment
Janda et al., 2021	Australia and New Zealand December 2012 to October 2019	Females over the age of 18 years with histologically confirmed EHA or FIGO grade 1 endometrioid EAC apparently confined to the uterus and with a BMI >30 kg/m^2, who wished to maintain fertility or who were at high risk of surgical complications due to severe medical co-morbidities Exclusion criteria: ECOG score >3; FIGO grade 2 or 3 endometrial cancer; histological cell type other than endometrioid; evidence of extrauterine disease on medical imaging; or received oral or intrauterine progestins prior to 12 weeks before planned randomization.	LNG-IUD (releasing 52 mg of levonorgestrel at a rate of 20 µg/24 h) Randomly assigned to (i) Observation (OBS); (ii) weight loss intervention (WL); or (iii) oral metformin (M) Participants assigned to the M arm had 500 mg of metformin orally, twice daily with meals (self-administered).	LNG-IUS + metformin N = 47	LNG-IUS + observation N = 35	Proportion of patients with pathological complete response pCR at six months from randomization (data on 3 months clearance also available)
Yuan et al., 2022	China Department of Obstetrics, Shaanxi Provincial People's Hospital, Xi'an, China	The inclusion criteria were set as follows: (1) **Endometrioid well-differentiated adenocarcinoma** diagnosed by histopathological examination after operation. (2) Patients with involved myometrium <1/2 and no extra-uterine lesions and lymph node metastasis by MRI. (3) Those who were aged <40 years old, nulliparous, and still had the willingness to bear children. (4) Those with estrogen-dependent and progesterone receptor (PR)-positive endometrial cancer.	MPA 0.4-0.8 g/day MPA 0.4-0.80 g/day + Metformin 0.5 g/time 3x a day	MPA + metformin N = 60 Age 33.73 ± 7.47 BMI 34.43 ± 4.24	MPA N = 60 Age 35.12 ± 8.41 BMI 33.37 ± 4.49	1. Clinical efficacy at 16 weeks 2. Adverse reaction 3. Pregnancy outcomes

clearance rate of atypical endometrial hyperplasia and early-stage endometrial cancer at 12-16 weeks. For endometrial hyperplasia without atypia, there appears to be an increase in clearance rates at 12-16 weeks OR 5.12 (95% CI 1.13, 22.41; n = 102) when compared to progesterone monotherapy (Figure 4).

Using GRADEpro Guideline Development Tool, metformin added to progesterone in patients with endometrial hyperplasia without atypia may increase clearance rates at 12-16 weeks, but the quality of evidence is very low because of a high risk of bias and imprecision. The anticipated absolute risk difference for clearance rate is 142 more per 1,000 patients (95% CI 22-174 more) in patients with endometrial hyperplasia without atypia.

Relapse Rates

Only one RCT looked at relapse rates after 12 months of clearance. Based on Yang 2020, adjunctive metformin does not decrease the relapse rates as compared to progesterone monotherapy alone for atypical endometrial hyperplasia and early-stage endometrial cancer (OR 0.89, 95%CI 0.28, 2.79; n = 135) (Figure 5). The certainty of the evidence is very low because of the high risk of performance and detection bias and imprecision.

Secondary Outcomes

Clinical Pregnancy Rate

Two studies examined the clinical pregnancy rates after adjunctive metformin (Yang 2020 and Yuan 2022). Based on these two studies, adjunctive metformin does not increase pregnancy rates as compared to progesterone monotherapy (OR 1.61, 95% CI 0.53, 4.89; n = 188) (Figure 6); this is based on very low certainty of evidence because of serious risk of bias and imprecision.

Live Birth Rate

The two studies that looked at clinical pregnancy rates also compared the live birth rates after adjunctive metformin (Yang 2020 and Yuan 2022). Based on these two studies, metformin with progesterone increases the live birth rates OR 2.51 (95% CI 1.34, 4.69; n = 188) (Figure 7) compared to progesterone monotherapy. The anticipated absolute effect is 225 more live births per 1000 cases (9% CI 73, 352). This

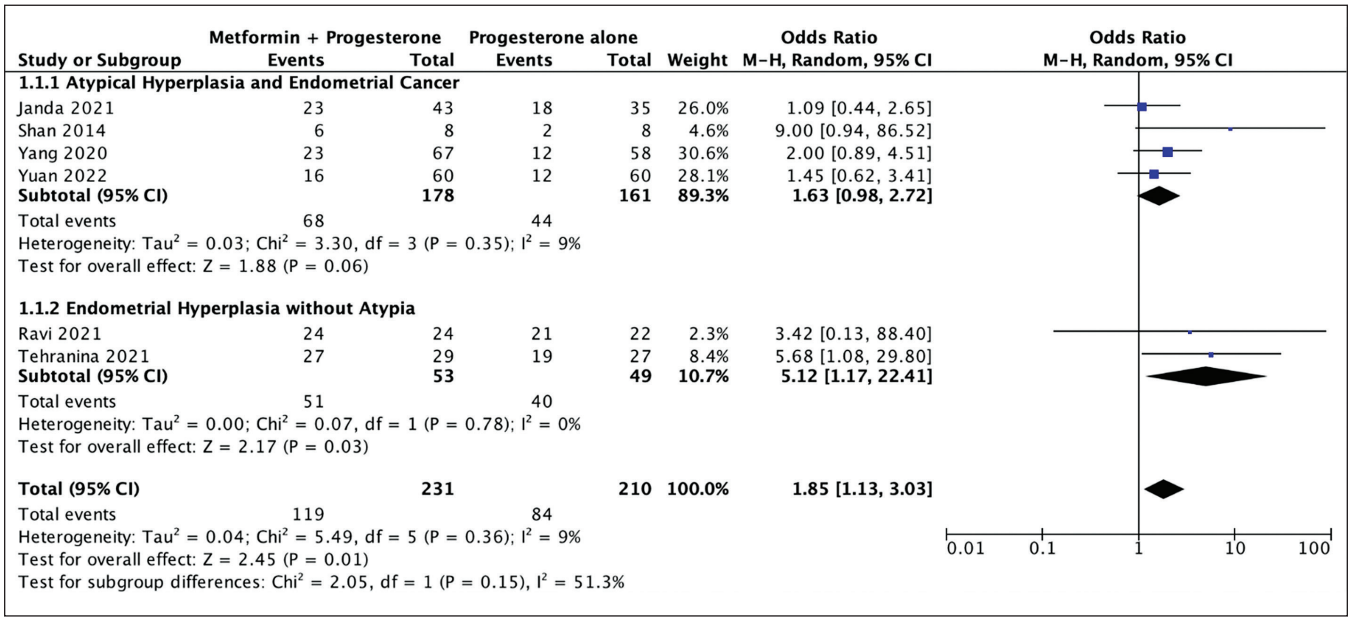

Figure 4. Forest plot of the effect of adjunctive metformin on clearance rates at 12-16 weeks.

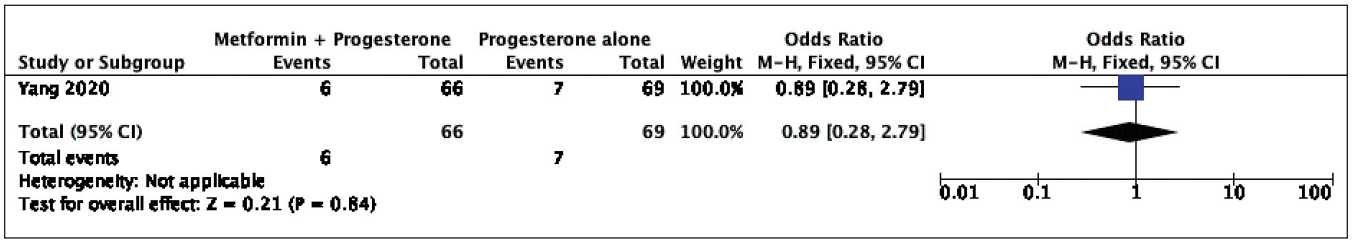

Figure 5. Forest plot of the effect of adjunctive metformin on relapse rates after 12 months.

is based on low-certainty evidence because of the high risk of bias for the two studies.

DISCUSSION

Summary of Main Results

Evidence from six studies demonstrates a possible benefit of adjunctive metformin in clearance rates at 12-16 week of endometrial hyperplasia, but not atypical endometrial hyperplasia and endometrial cancer, as compared to progesterone monotherapy, but the evidence is uncertain. Metformin does not appear to decrease the incidence of relapse after 12 months. For the secondary outcomes, there is a trend of increasing live birth rates in patients given adjunctive metformin, but the evidence is uncertain. The certainty of the evidence was downgraded because of the substantial risk of bias associated with the open-label design, as well as the wide confidence intervals observed both across the individual studies and in the pooled effects. The summary of findings is summarized in Table 2.

Interpretation of Results

Metformin is an oral anti-diabetic agent belonging to the class of biguanides. Metformin enhances the phosphorylation and activation of AMPK, which in turn leads to the inhibition of hepatic gluconeogenesis (glucose production in the liver) and the promotion of glucose uptake in peripheral tissues, such as skeletal muscle. In addition to its effects on glucose metabolism, metformin has been shown to modulate various signaling pathways implicated in cellular growth and proliferation.[13] For instance, it can inhibit the mammalian target of rapamycin (mTOR) pathway, which plays a crucial role in regulating cell growth and protein synthesis. By inhibiting mTOR, metformin attenuates the aberrant cell proliferation observed in endometrial cancer lines.[14] Metformin has also been shown to increase progesterone receptor expression in endometrial cell lines and has been theorized to contribute to better clinical response.[15]

Several observational studies have investigated the potential role of metformin in fertility sparing treatment of endometrial hyperplasia and endometrial cancer. In 2013, a study by Korkmaz et al. showed that metformin may be used as an adjunct to medroxyprogesterone acetate for the treatment of endometrial hyperplasia; there were significantly less cases of refractory hyperplasia in the group who received adjunctive metformin.[16] In infertile women with complex hyperplasia and complex hyperplasia with atypia, regression is improved by metformin plus progesterone compared with progesterone monotherapy; a subgroup analysis showed the effect to be more pronounced in patients with BMI ≥25 kg/m^2 and patients with polycystic ovary syndrome. However, there was no significant effect on fertility outcomes for those on combination metformin and progesterone.[17] Another retrospective cohort study on patients with atypical endometrial hyperplasia and early-stage endometrial cancer showed increase relapse free survival and pregnancy outcome in the combination therapy group; the effect more notable in those with BMI ≥25 kg/m^2.[18] A 2020 single institution retrospective study on progestin routes and adjunctive metformin showed that metformin improved remission rates of endometrial hyperplasia in patients with the levonorgestrel IUD but not for those taking oral progestins.[19]

A 2021 systematic review and meta-analysis of observational studies that investigated the effect of combined metformin and progesterone on atypical endometrial hyperplasia and early-stage endometrial cancer concluded

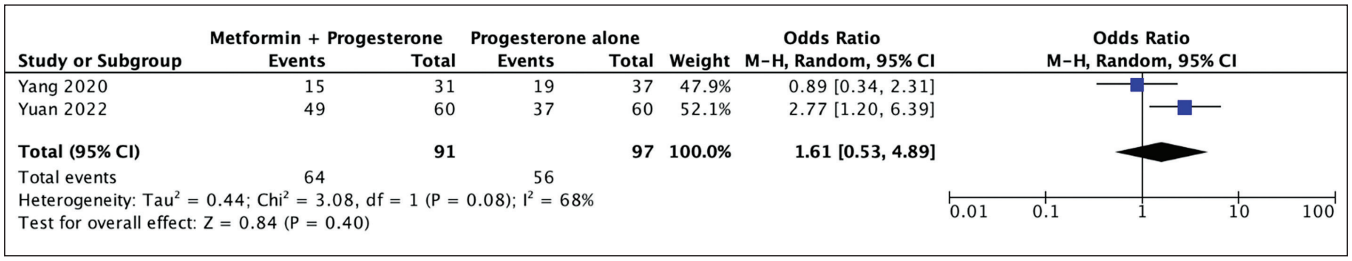

Figure 6. Forest plot of the effect of adjunctive metformin on clinical pregnancy rates.

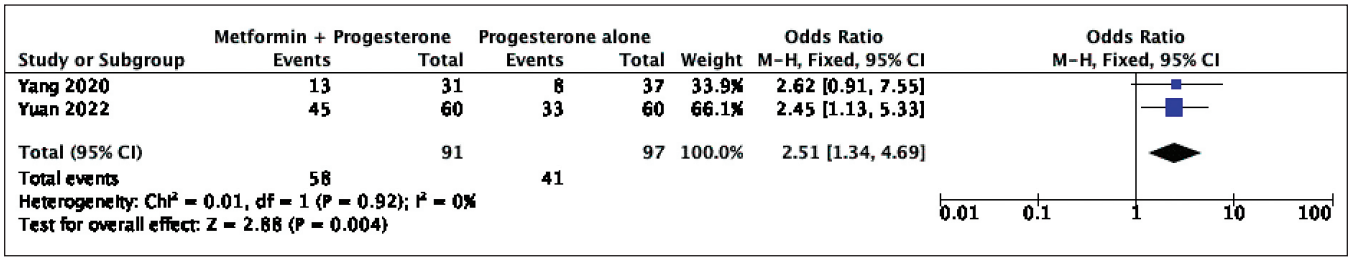

Figure 7. Forest plot of the effect of adjunctive metformin on live birth rates.

that combined treatment may decrease relapse rates but had no effect on clinical remission and fertility outcomes.[6] This systematic review and meta-analysis of randomized controlled trials aimed to provide better quality evidence for the effect of combined treatment of progesterone and metformin in cases of endometrial hyperplasia and endometrial cancer. The authors wanted to confirm if the findings of the previous systematic review of observational studies, no significant effect for clinical remission and pregnancy outcomes and decrease in relapse rate, also holds true for the randomized controlled trials.

The differential response in clinical remission rates between endometrial hyperplasia and atypical hyperplasia and endometrial cancer can be explained by the different impact of metformin on nuclear atypia. Endometrial carcinoma is also a heterogenous disease with varying subtypes that may

Table 2. Summary of Findings

Metformin + Progesterone compared to Progesterone alone for Endometrial hyperplasia and carcinoma

Patient or population: Endometrial hyperplasia and carcinoma
Intervention: Metformin + Progesterone
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Progesterone Alone	Risk with Metformin + Progesterone				
Complete Response at 12-16 weeks	400 per 1,000	**552 per 1,000** (430 to 669)	**OR 1.85** (1.13 to 3.03)	441 (6 RCTs)	⨁◯◯◯ Very low[a,b]	Metformin + Progesterone may increase/have little to no effect on complete response at 12-16 weeks but the evidence is very uncertain.
Complete Response at 12-16 weeks – Atypical Hyperplasia and Endometrial Cancer	273 per 1,000	**380 per 1,000** (269 to 506)	**OR 1.63** (0.98 to 2.72)	339 (4 RCTs)	⨁◯◯◯ Very low[a,b]	Metformin + Progesterone does not increase complete response rates in patients with atypical hyperplasia and endometrial cancer.
Complete Response at 12-16 weeks – Endometrial Hyperplasia without Atypia	816 per 1,000	**958 per 1,000** (839 to 990)	**OR 5.12** (1.17 to 22.41)	102 (2 RCTs)	⨁◯◯◯ Very low[a,c]	Metformin + Progesterone may increase/have little to no effect on complete response at 12-16 weeks - Endometrial Hyperplasia without Atypia but the evidence is very uncertain.
Relapse at 12 mos	101 per 1,000	**91 per 1,000** (31 to 240)	**OR 0.89** (0.28 to 2.79)	135 (1 RCT)	⨁◯◯◯ Very low[d,e]	Metformin + Progesterone does not affect relapse rates.
Clinical Pregnancy	577 per 1,000	**687 per 1,000** (420 to 870)	**OR 1.61** (0.53 to 4.89)	188 (2 RCTs)	⨁◯◯◯ Very low[f,g]	Metformin + Progesterone does not affect clinical pregnancy rates.
Live Birth Rate	423 per 1,000	**648 per 1,000** (495 to 774)	**OR 2.51** (1.34 to 4.69)	188 (2 RCTs)	⨁⨁◯◯ Low[f]	The evidence suggests metformin + progesterone results in a slight increase in live birth rate.

***The risk in the intervention group** (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; **OR:** odds ratio

GRADE Working Group grades of evidence
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 effect.

Explanations:
[a] *Downgraded by two levels for very serious risk of bias: there was no detailed random sequence generation or allocation concealment or blinding; studies were also at high risk of attrition bias.*
[b] *Downgraded by one level for very serious imprecision: studies have very small sample sizes, and confidence intervals are wide.*
[c] *Downgraded by two levels for very serious imprecision: the confidence interval of the pooled results is very wide.*
[d] *Only Yang 2020 looked at relapse rates and this study is subject to a high risk of bias because of performance and detection bias*
[e] *Confidence intervals that pass the line of no significance.*
[f] *Downgraded by two levels for very serious risk of bias: for Yuan 2022, no detailed random sequence generation or allocation concealment; participants and personnel were not blinded.*
[g] *Downgraded by one level for serious imprecision because of the small sample size and wide confidence interval that crosses the line of no effect.*

exhibit different molecular characteristics which may be less susceptible to the effects of metformin.

Certainty of Evidence

Using GRADEpro, we determined the certainty of the current evidence for the effect of metformin added to progesterone on clearance, relapse, pregnancy, and live birth rates in patients with endometrial hyperplasia and early-stage endometrial cancer to be very low to low.

The findings of this systematic review are based on six randomized controlled trials, of which four were open-label in design, thereby introducing a high risk of bias with respect to the blinding of participants and personnel. Given the limited sample sizes and the low incidence of observed events in these trials, the pooled results are less precise, as evidenced by the wide confidence intervals.

Implications for Research

The results from this study provides an opportunity to undertake a randomized controlled trial in Filipinas with endometrial hyperplasia to ascertain whether analogous effects can also be observed in the Filipino population. Further research into the molecular mechanisms underlying the improved response rate observed in patient with endometrial hyperplasia given adjunctive metformin could provide better foundation for metformin's efficacy.

Potential Biases in the Review Process

Literature search was limited to articles published in the English language.

CONCLUSIONS

The current practice recommendations do not support the use of metformin as an adjunct to progesterone in the treatment of endometrial hyperplasia, atypical endometrial hyperplasia, and endometrial cancer. Although this review identified potential benefits in achieving clinical remission among patients with endometrial hyperplasia without atypia, the certainty of evidence remains very low. This is primarily attributed to the open-label design of many of the included studies, inconsistent results across studies, and wide confidence intervals observed in the pooled outcomes. To establish more robust practice recommendations, future research endeavors should prioritize high-quality trials that can provide more compelling evidence.

Availability of Data Collection Forms

Data collection forms and extracted data are available upon request to the corresponding author.

Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

Both authors declared no conflicts of interest.

Funding Source

None.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021 May;71(3):209–49. doi: 10.3322/caac.21660. PMID: 33538338.
2. Pellerin GP, Finan MA. Endometrial cancer in women 45 years of age or younger: A clinicopathological analysis. Am J Obstet Gynecol. 2005 Nov;193(5):1640–4. doi: 10.1016/j.ajog.2005.05.003. PMID: 16260203.
3. Lortet-Tieulent J, Ferlay J, Bray F, Jemal A. International patterns and trends in endometrial cancer incidence, 1978–2013. J Natl Cancer Inst. 2018 Apr 1;110(4):354–61. doi: 10.1093/jnci/djx214. PMID: 29045681.
4. Ring KL, Mills AM, Modesitt SC. Endometrial hyperplasia. Obstet Gynecol. 2022 Dec 1;140(6):1061–75. doi: 10.1097/AOG.0000000000004989. PMID: 36357974.
5. Contreras NA, Sabadell J, Verdaguer P, Julià C, Fernández-Montolí ME. Fertility-Sparing approaches in atypical endometrial hyperplasia and endometrial cancer patients: current evidence and future directions. Int J Mol Sci. 2022 Feb 25;23(5):2531. doi: 10.3390/ijms23052531. PMID: 35269674; PMCID: PMC8910633.
6. Chae-Kim J, Garg G, Gavrilova-Jordan L, Blake LE, Kim TT, Wu Q, et al. Outcomes of women treated with progestin and metformin for atypical endometrial hyperplasia and early endometrial cancer: a systematic review and meta-analysis. Int J Gynecol Cancer. 2021 Dec;31(12):1499–505. doi: 10.1136/ijgc-2021-002699. PMID: 34785524.
7. Ravi RD, Kalra J, Srinivasan R, Bagga R, Jain V, Suri V, et al. A randomized clinical trial of levonorgestrel intrauterine system with or without metformin for treatment of endometrial hyperplasia without atypia in Indian women. Asian Pac J Cancer Prev. 2021 Mar 1;22(3):983–9. doi: 10.31557/APJCP.2021.22.3.983. PMID: 33773565; PMCID: PMC8286694.
8. Shan W, Wang C, Zhang Z, Gu C, Ning C, Luo X, et al. Conservative therapy with metformin plus megestrol acetate for endometrial atypical hyperplasia. J Gynecol Oncol. 2014 Jul;25(3):214-20. doi: 10.3802/jgo.2014.25.3.214. PMID: 25045434; PMCID: PMC4102740.
9. Yuan F, Hu Y, Han X, Li Q. Metformin in combination with progesterone improves the pregnancy rate for patients with early endometrial cancer. Hashmi MF, editor. Contrast Media Mol Imaging. 2022 Jul 6;2022:1961016. doi: 10.1155/2022/1961016. PMID: 35854762; PMCID: PMC9279044.
10. Yang B, Gulinazi Y, Du Y, Ning C, Cheng Y, Shan W, et al. Metformin plus megestrol acetate compared with megestrol acetate alone as fertility-sparing treatment in patients with atypical endometrial hyperplasia and well-differentiated endometrial cancer: a randomised controlled trial. BJOG. 2020 Jun;127(7):848–57. doi: 10.1111/1471-0528.16108. PMID: 31961463.
11. Tehranian A, Ghahghaei-Nezamabadi A, Arab M, Khalagi K, Aghajani R, Sadeghi S. The impact of adjunctive metformin to progesterone for the treatment of non-atypical endometrial hyperplasia in a randomized fashion, a placebo-controlled, double blind clinical trial. J Gynecol Obstet Hum Reprod. 2021 Jun;50(6):101863. doi: 10.1016/j.jogoh.2020.101863. PMID: 32652300.
12. Janda M, Robledo KP, Gebski V, Armes JE, Alizart M, Cummings M, et al. Complete pathological response following levonorgestrel intrauterine device in clinically stage 1 endometrial adenocarcinoma: Results of a randomized clinical trial. Gynecol Oncol. 2021 Apr;161(1):143–51. doi: 10.1016/j.ygyno.2021.01.029. PMID: 33762086.

13. Aljofan M, Riethmacher D. Anticancer activity of metformin: a systematic review of the literature. Future Sci OA. 2019 Aug 22;5(8):FSO410. doi: 10.2144/fsoa-2019-0053. PMID: 31534778; PMCID: PMC6745597.
14. Cantrell LA, Zhou C, Mendivil A, Malloy KM, Gehrig PA, Bae-Jump VL. Metformin is a potent inhibitor of endometrial cancer cell proliferation—implications for a novel treatment strategy. Gynecol Oncol. 2010 Jan;116(1):92–8. doi: 10.1016/j.ygyno.2009.09.024. PMID: 19822355; PMCID: PMC2789879.
15. Collins G, Mesiano S, DiFeo A. Effects of metformin on cellular proliferation and steroid hormone receptors in patient-derived, low-grade endometrial cancer cell lines. Reprod Sci. 2019 May;26(5): 609–18. doi: 10.1177/1933719118779734. PMID: 29848180.
16. Korkmaz V, Ozkaya E,Kucukozkan T, Kara F, Cekmez Y, Korkmaz H. Medroxyprogesterone acetate plus metformin to prevent persistent endometrial hyperplasia. Gynecol Obstet Reprod Med. 2013;19: 96-9.
17. Kong W, Liu Z, Zhang N, Wu X, Zhao X, Yan L. A prospective cohort study of metformin as an adjuvant therapy for infertile women with endometrial complex hyperplasia/complex atypical hyperplasia and their subsequent assisted reproductive technology outcomes. Front Endocrinol. 2022 Jun 30;13:849794. doi: 10.3389/fendo. 2022.849794. PMID: 35846327; PMCID: PMC9280669.
18. Mitsuhashi A, Habu Y, Kobayashi T, Kawarai Y, Ishikawa H, Usui H, et al. Long-term outcomes of progestin plus metformin as a fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer patients. J Gynecol Oncol. 2019 Nov;30(6):e90. doi: 10.3802/jgo.2019.30.e90. PMID: 31576686; PMCID: PMC6779615.
19. Matsuo K, Mandelbaum RS, Ciccone M, Khoshchehreh M, Purswani H, Morocco EB, et al. Route-specific association of progestin therapy and concurrent metformin use in obese women with complex atypical hyperplasia. Int J Gynecol Cancer. 2020 Sep; 30(9):1331–9. doi: 10.1136/ijgc-2020-001362. PMID: 32376736; PMCID: PMC7521080.