

# Effects of dyslipidemia on fertility-sparing treatment outcomes in endometrial atypical hyperplasia and endometrial cancer: a large cohort study

Received: 10 October 2024

Accepted: 27 March 2026

Published online: 03 April 2026

Cite this article as: Luo S., Wang M., Shan W. *et al.* Effects of dyslipidemia on fertility-sparing treatment outcomes in endometrial atypical hyperplasia and endometrial cancer: a large cohort study. *Sci Rep* (2026). <https://doi.org/10.1038/s41598-026-46711-7>

Shuhan Luo, Manrong Wang, Weiwei Shan, Lulu Wang, Sijia Liu, Qujia Gama, Xuezhen Luo & Pengfei Wu

We are providing an unedited version of this manuscript to give early access to its findings. Before final publication, the manuscript will undergo further editing. Please note there may be errors present which affect the content, and all legal disclaimers apply.

If this paper is publishing under a Transparent Peer Review model then Peer Review reports will publish with the final article.

**Effects of dyslipidemia on fertility-sparing treatment outcomes in endometrial atypical hyperplasia and endometrial cancer: a large cohort study**

Shuhan Luo <sup>a, □</sup>, Manrong Wang <sup>a, □</sup>, Weiwei Shan <sup>a</sup>, Lulu Wang <sup>a</sup>, Sijia Liu <sup>a</sup>, Qujia Gama <sup>a</sup>, Xuezhen Luo <sup>a,b,\*</sup>, Pengfei Wu <sup>a,b,\*</sup>

<sup>a</sup>Department of Gynecology, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China

<sup>b</sup>Shanghai Key Laboratory of Female Reproductive Endocrine Related Diseases, Shanghai, China

□ Shuhan Luo and Manrong Wang equally contributed to this study and were the first authors.

**\*Corresponding Author:**

Xuezhen Luo, Department of Gynecology, Obstetrics and Gynecology Hospital of Fudan University, 419 Fangxie Road, Shanghai 200011, China. E-mail: xuezhenluo2013@163.com

Pengfei Wu, Department of Gynecology, Obstetrics and Gynecology Hospital of Fudan University, 419 Fangxie Road, Shanghai 200011, China. E-mail: leofinger@163.com

**Abstract**

**Objective**

This study aimed to investigate the impact of dyslipidemia on outcomes of fertility-preserving treatment in patients with endometrioid endometrial cancer (EEC) or endometrial atypical hyperplasia (EAH).

**Methods**

A total of 406 patients, including 118 EEC and 288 EAH, who received fertility-sparing treatment between January 2017 and December 2020 were included and divided into a dyslipidemia group (n=282) and a non-dyslipidemia group (n=124). The 16-/32-week complete response (CR) rate, pregnancy outcome, and recurrence were compared between patients with and without dyslipidemia. Furthermore, we explored the effect of different indicators of dyslipidemia, including total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL), on the therapeutic effects of fertility-preserving treatment.

## Results

A total of 282 (69.5%) patients were diagnosed with dyslipidemia, and 38 patients were diagnosed with mixed dyslipidemia. The 16-/32-week CR rate, pregnant rate, live birth rate, and recurrence did not have significant differences between patients with and without dyslipidemia. Patients with mixed dyslipidemia had a lower 32-week CR rate (42.1% vs.65.5%,  $P=0.004$ ) and a longer treatment duration to achieve CR (33.4 weeks vs. 27.0 weeks,  $P=0.039$ , HR: 0.73, 95%CI: 0.53-0.98) than those without mixed dyslipidemia. Multivariate logistic regression analyses demonstrated that mixed dyslipidemia was significantly associated with a lower 32-week CR rate (OR: 0.322, 95% CI: 0.134-0.775,  $P=0.011$ ). Patients with both overweight and mixed dyslipidemia had the lowest 32-week CR rate (12/31, 38.5%,  $P=0.007$ ) and longest median treatment duration to CR (34.0 weeks, 95%CI: 25.7-42.3 weeks,  $P=0.025$ ).

## Conclusion

Mixed dyslipidemia was an independent risk factor for fertility-preserving treatment outcomes in EAH or EEC patients, as this group had a lower 32-week CR rate and a longer treatment duration to achieve CR than those without mixed dyslipidemia.

**Keywords:** endometrial atypical hyperplasia; endometrial cancer; conservative treatment; dyslipidemia; mixed dyslipidemia

### **Introduction**

Endometrial cancer (EC) is one of the most common gynecological malignancies, and the rate of progression of endometrial atypical hyperplasia (EAH) to cancer is nearly 25%[1]. Progestin and hysteroscopy in fertility-preserving treatment has recently become particularly important for endometrioid EC (EEC) and EAH patients[2]. Dyslipidemia refers to abnormal lipid metabolism characterized by any one of hypercholesterolemia, high-density lipoprotein (HDL)-hypocholesterolemia, low-density lipoprotein (LDL)-hypercholesterolemia, and hypertriglyceridemia. Dyslipidemia is common in EEC or EAH patients seeking fertility-preserving treatment[3].

Recently, many risk factors have been linked to the complete response (CR) rate of EEC and EAH patients—including overweight and insulin resistance[4, 5]. A previous study showed that dyslipidemia was significantly associated with worse overall survival and recurrence-free survival of EC patients[6]. Additionally, the use of statins, which are widely prescribed to treat hypercholesterolemia, has been shown to improve survival of EC patients[7]. However, few studies have explored the effects of dyslipidemia and its components on the outcome of fertility-preserving treatment in EEC and EAH.

In this retrospective cohort study, we aimed to assess the effects of both dyslipidemia as a whole and its individual components on the efficacy of

fertility-preserving treatment in EEC and EAH patients.

## **Materials and methods**

### **1. Study population**

Our retrospective study investigated 662 consecutive patients who received fertility-sparing treatment at the Obstetrics and Gynecology Hospital of Fudan University between January 2017 and December 2020. All included patients underwent standardized evaluation and treatment based on progestin. During the treatment and follow-up, necessary information was prospectively collected and recorded. All patients signed informed consent for the treatment and the use of their data for research purposes before enrollment. The retrospective study was approved by the Ethics Committee of the Obstetrics and Gynecology Hospital of Fudan University (No. 2022-203). All experiments were performed in accordance with relevant guidelines and regulations.

The inclusion and exclusion criteria for conservative treatment strictly followed National Comprehensive Cancer Network guidelines[8]. The inclusion criteria were as follows: 1) pathologically proven EAH or well-differentiated EEC G1 without myometrial invasion or lymphatic vascular infiltration; 2) no evidence of suspicious extrauterine metastasis based on enhanced magnetic resonance imaging, enhanced computed tomography or ultrasound; 3) younger than 45 years old at diagnosis; 4) a strong willingness to preserve fertility; 5) no contraindications for treatment; and 6) good compliance for treatment and follow-up. To minimize potential bias treatment in efficacy due to the progestin treatment period, patients who used local or systematic progestins for more than one month before primary comprehensive evaluation at our center were excluded from this study.

### **2. Pathological diagnosis**

All patients were pathologically diagnosed by endometrial biopsy through dilation and curettage with or without hysteroscopy. Pathological diagnosis was

confirmed by two experienced gynecological pathologists based on the World Health Organization pathological classification (2014). A seminar was held to determine the final diagnosis if their opinions differed. If the patient was initially diagnosed without hysteroscopy, a hysteroscopy was performed to confirm the diagnosis within one month following the initial pathological diagnosis.

### 3. Conservative treatment and evaluation

Fertility-preserving treatment was initiated immediately after the comprehensive evaluation was completed. The therapeutic regimens were determined by experienced gynecological doctors. Most patients received oral megestrol acetate (MA) at a dose of 160 mg/day. Others received a levonorgestrel-releasing intrauterine system (LNG-IUS) only or MA plus LNG-IUS. We did not prohibit the use of metformin (500mg thrice daily) and recorded the treatment regimens for each patient.

Therapeutic efficacy was evaluated every 3 months through hysteroscopic evaluation during treatment. All hysteroscopic evaluations were performed by a team of experienced gynecological surgeons. During the procedures, we use a standardized set of instruments and a uniform approach to visualize and assess the endometrial lesions. Endometrial lesions were removed during the hysteroscopic evaluation, and a random endometrium biopsy was performed if no obvious lesion was observed. If there are any questions in hysteroscopic evaluation, a second independent observer was involved in reviewing the video recordings of the procedures and confirming the findings.

The response to the treatment was determined histologically by assessing specimens obtained from each hysteroscopic evaluation. CR was defined as no hyperplasia or cancerous lesion. Partial response (PR) was defined as the presence of hyperplasia without atypia for all patients or atypical hyperplasia for EEC patients; stable disease (SD) was defined as persistence of the initially diagnosed lesion; and progressive disease (PD) was defined as the observation of EEC in patients with EAH or evidence of more severe pathological lesions,

myometrial invasion or extrauterine metastasis in EEC patients.

Patients were treated with the same regimen for another 2–3 months for consolidation after achieving CR. Another complete hysteroscopic evaluation was performed 3 months after the first CR to confirm the diagnosis. The treatment duration to achieve CR was calculated from the initiation of treatment to the time of their first pathological CR diagnosis. All patients desiring fertility were encouraged to get pregnant as soon as achieving CR and assisted reproductive treatments were recommended. For patients who did not have a parental plan, oral contraceptive pills or LNG-IUS were used to prevent recurrences. Patients were followed up every 3 to 6 months after CR with ultrasound evaluation and were pathologically evaluated with an endometrial biopsy using Pipelle every 6 months.

Definitive hysterectomy was strongly recommended if any of the follows occurred: 1) SD continued for 6 months; 2) PR continued for 9 months; 3) PD appeared at any time. For patients who refused definitive hysterectomy, alternative treatments were given according to the recommendations of a multidisciplinary team.

#### 4. Data collection

General information including age at diagnosis, height, weight, basic blood pressure and comorbidities (e.g., hypertension or diabetes) and blood samples were collected before initiating fertility-preserving treatment. The body mass index (BMI) was calculated as  $\text{weight (kg)/height}^2 \text{ (m}^2\text{)}$ .  $\text{BMI} \geq 25 \text{ kg/m}^2$  was defined as overweight[9].

All blood samples were collected and examined in the laboratory of the Obstetrics and Gynecology Hospital of Fudan University. Fasting insulin, fasting blood glucose, lipid profiles were measured. Diagnosis of dyslipidemia and mixed dyslipidemia were based on the 2016 Chinese guideline for the management of dyslipidemia in adults[10]. A diagnosis of dyslipidemia was made if at least one of the following criteria was met: (1) Total cholesterol (TC) > 5.2 mmol/L; (2)

Triglycerides (TG) > 1.7 mmol/L; (3) High-density lipoprotein cholesterol (HDL-C) < 1.0 mmol/L; (4) Low-density lipoprotein cholesterol (LDL-C) > 3.4 mmol/L. Mixed dyslipidemia was defined as an elevation in both TC and TG above the thresholds specified above [10, 11]. The homeostasis model assessment-insulin resistance (HOMA-IR) index (fasting blood glucose [mmol/L] × fasting insulin [microU/mL]/22.5) was used to evaluate IR status[12]. HOMA-IR index ≥ 2.95 were considered as insulin resistant[13]. Patients were diagnosed with metabolic syndrome (MS) when they met any three of the following criteria: 1) waist circumference ≥ 80 cm, 2) triglycerides (TGs) ≥ 150 mg/dL or patients on treatment for elevated TGs, 3) high-density lipoprotein cholesterol (HDL-C) < 50 mg/dL or patients on treatment for reduced HDL-C, 4) elevated blood pressure: systolic pressure ≥ 130 mmHg and/or diastolic pressure ≥ 85 mmHg or patients on antihypertensive treatment, and 5) FBG ≥ 100 mg/dL or patients on treatment for elevated FBG[5].

## 5. Statistical analysis

The descriptive variables were presented as mean and standard deviation or median and range. The categorical variables were presented as frequency and percentage. The differences in the descriptive variables between the two groups were analyzed by the Student's t-test or Mann-Whitney U test. The Chi-square test or Fisher's exact test was used to analyze the differences in the categorical variables as appropriate. The treatment duration was estimated using Kaplan-Meier method; differences between groups were compared using log-rank test. Adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated with a univariate and multivariate logistic regression model for analyses of the relationship between covariates and 32-week CR. **As this was a retrospective study, no a priori sample size calculation was performed, and the sample size was determined by the number of eligible patients available in the database. A post-hoc power analysis was conducted for the primary endpoint (32-week CR) using a two-sided  $\alpha$  level of 0.05.  $p < 0.05$  in two-sided tests was**

considered statistically significant. Statistical analyses were performed using SPSS (version 23.0, IBM, Armonk, NY, USA).

## Results

### 1. General characteristics of patients

A total of 662 consecutive patients receiving fertility-preserving treatment at the Obstetrics and Gynecology Hospital of Fudan University between January 2017 and December 2020 were retrospectively investigated in our study (**Figure 1**). Overall, 256 patients were excluded, including 155 patients who received progestin treatment for more than one month before their first endometrial evaluation at our center, 43 patients who refused to be followed or were transferred to other hospitals before the first evaluation, 46 patients who quit conservative treatment and required surgery before the first hysteroscopy, 12 patients with insufficient clinical information for the diagnosis of dyslipidemia. Ultimately, 406 patients (288 EAH patients and 188 EEC G1 patients) were included in this study. None of the patients received pharmacological lipid-lowering treatments, such as statins, nor did they undergo medical intervention for lifestyle management during their fertility-preserving treatment. The general characteristics of these patients are presented in **Table 1**. 282 (69.5%) patients were diagnosed with dyslipidemia, and 38 (13.5%) patients were diagnosed with mixed dyslipidemia among these 282 patients. The median age at diagnosis was 32 years old. Patients with dyslipidemia had higher rates of IR (42.9% vs. 30.6%,  $p=0.020$ ), MS (40.4% vs. 24.2%,  $p=0.002$ ) and diabetes mellitus (12.4% vs. 5.6%,  $p=0.038$ ) than those without dyslipidemia. Among the 406 patients, 158 were treated with MA, 85 were treated with MA plus MET, 78 with IUD alone, 12 with MA plus IUD and 73 with MA plus IUD and MET. No significant differences were found in age, BMI, hypertension, parity, pathological diagnosis, and treatment methods between patients with and without dyslipidemia.

## 2. Effects of dyslipidemia on fertility-preserving treatment outcome

The outcome of fertility-preserving treatment is summarized in **Table 2**, **Supplementary Table 1** and **Supplementary Table 2**. The median follow-up time from patients receiving treatment to our final follow-up time point was 76.5 weeks (range, 13.0 to 176.0 weeks). The 16-week CR rate (27.0% vs. 28.2%) and 32-week CR rate (61.7% vs. 66.9%) were both lower in patients with dyslipidemia than those without dyslipidemia. However, the 16-/32-week CR rate was higher in EEC patients with dyslipidemia. In patients with dyslipidemia, the differences in CR rates and treatment duration were not statistically significant across the regimens (**Supplementary Table 1**). Patients with dyslipidemia took a longer duration to achieve CR (28.3 weeks vs. 26.1 weeks,  $P=0.180$ , hazard ratio (HR): 0.86, 95%CI: 0.68-1.08) (**Figure 2**). 59 (44.0%) patients were pregnant among 134 patients who attempted pregnancy after achieving CR and among those patients who achieved pregnancy, 36 (61%) patients had live birth in total. However, there were no significant differences in 16-/32-week CR rate, treatment duration to achieve CR, pregnant rate, live birth rate, the time-to-pregnancy, pregnancy complications and recurrent rate between patients with and without dyslipidemia.

We then performed univariate and multivariate logistic regression analyses to determine whether different indicators of dyslipidemia, including TC, TG, HDL, and LDL, were related to 16-/32-week CR in EAH and EEC patients receiving fertility-preserving treatment (**Table 3**). There was no significant effect on 16-/32-week CR in EAH and EEC patients in TC, TG, HDL, or LDL.

## 3. Effects of mixed dyslipidemia on fertility-preserving treatment outcome

The effects of mixed dyslipidemia on the outcome of the fertility-sparing treatment were shown in **Figure 3** and **Table 3**. Patients with mixed dyslipidemia had a lower 16-week CR rate (21.1% vs. 28.0%) than those without mixed dyslipidemia, but it did not have a significant difference. The 32-week CR rate was significantly lower in patients with mixed dyslipidemia than those

without mixed dyslipidemia (42.1% vs. 65.5%,  $P=0.004$ ). Patients in the mixed dyslipidemia group had a longer treatment duration to achieve CR (33.4 weeks vs. 27.0 weeks,  $P=0.039$ , HR: 0.73, 95%CI: 0.53-0.98). To isolate the effects of dyslipidemia and MS more clearly, we performed a stratified analysis by MS status, dividing patients into MS and non-MS groups. While these differences were not statistically significant, the results showed that, regardless of MS status, patients with mixed dyslipidemia had a longer median time to achieve CR (data not showed). In the MS group: 33.4 weeks for mixed dyslipidemia patients vs. 26.3 weeks for non-mixed dyslipidemia patients. In the non-MS group: 36.4 weeks for mixed dyslipidemia patients vs. 27.0 weeks for non-mixed dyslipidemia patients.

We then evaluated mixed dyslipidemia and other possible risk factors affecting fertility-preserving treatment outcome with different logistic regression models in **Table 3**. The Crude model with unadjusted covariates showed that EEC (OR: 0.613, 95% CI: 0.396-0.950,  $P=0.029$ ), overweight (OR: 0.591, 95% CI: 0.393-0.889,  $P=0.012$ ), and mixed dyslipidemia (OR: 0.383, 95% CI: 0.194-0.756,  $P=0.006$ ) were significantly associated with lower 32-week CR rate. In Model 1 adjusted for age at diagnosis, overweight, pathological diagnosis, and mixed dyslipidemia, the result indicated that EEC (OR: 0.580, 95% CI: 0.369-0.913,  $P=0.018$ ), and mixed dyslipidemia (OR: 0.408, 95% CI: 0.201-0.826,  $P=0.013$ ) were significantly associated with lower 32-week CR rate. After adjustment for age at diagnosis, overweight, pathological diagnosis, HDL, LDL, IR, MS, hypertension, DM and/or progestin therapy in Model 2 and Model 3 mixed dyslipidemia was still significantly associated with lower 32-week CR rate (in Model 3, OR: 0.322, 95% CI: 0.134-0.775,  $P=0.011$ ).

We then stratified mixed dyslipidemia and non-mixed dyslipidemia patients according to BMI ( $BMI < 25 \text{ kg/m}^2$  and  $BMI \geq 25 \text{ kg/m}^2$ ) into four groups (**Figure 4**), the normal weight (NW) and non-mixed dyslipidemia (NMD) group, the overweight (OW) and NMD group, the NW and mixed dyslipidemia (MD) group, and the OW and MD group. In these groups, the 32-week CR rate ( $P=0.007$ ) and

median treatment duration to CR ( $P=0.025$ ) both had significant differences. Patients in the OW and MD group had the lowest 32-week CR rate (12/31, 38.5%) while those in the NW and NMD group had the highest 32-week CR rate (140/202, 69.3%). Patients in the OW and MD group had the longer median treatment duration to CR (34.0 weeks, 95%CI: 25.7-42.3 weeks) than those in the NW and NMD group (26.0 weeks, 95%CI: 22.2-29.8 weeks) and those in the OW and NMD group (29.0 weeks, 95%CI: 26.2-31.8 weeks). However, it achieved a significant difference only when compared with the NW and NMD group ( $P=0.007$ , HR: 0.63, 95%CI: 0.45-0.88).

## **Discussion**

Fertility-sparing treatment is usually applied for young patients with EAH and EEC who have a strong desire to retain fertility potential. While fertility-preserving treatments have been extensively studied for their efficacy and safety, there is limited research exploring the role of dyslipidemia in influencing treatment outcomes in EAH and EEC patients. This study aimed to address this gap by evaluating the impact of dyslipidemia, specifically mixed dyslipidemia, on the fertility-preserving treatment outcomes in patients with EAH and EEC.

Our findings reveal that dyslipidemia was prevalent in approximately 70% of the patients, aligning with previous studies showing high rates of metabolic abnormalities in patients with endometrial carcinoma[6, 14]. However, while dyslipidemia was common, none of its components had significant influences on short-term CR rates or reproductive outcomes in our cohort. Similar to our findings, previous studies have identified associations between lipid metabolism and other metabolic conditions such as insulin resistance and diabetes mellitus[15, 16]. However, no significant differences were observed in age, BMI, and hypertension between patients with and without dyslipidemia in our study.

Our study's specific focus on the impact of dyslipidemia, including mixed dyslipidemia, on fertility-preserving treatment outcomes adds a new dimension

to existing literature. Previous studies have shown that MS is associated with a longer time to achieve CR and a higher recurrence rate in patients with EAH and EEC undergoing fertility-sparing treatment [17, 18]. However, our study found no significant difference in CR rates between patients with and without MS. Interestingly, although not statistically significant, dyslipidemia, a feature of MS, trended towards a longer treatment duration to reach CR in our study. Differences in conclusions may be explained by different definitions of MS and sample sizes used in these studies.

A key finding in this study was the impact of mixed dyslipidemia, characterized by elevated TC and TG, on treatment outcomes. Patients with mixed dyslipidemia exhibited significantly lower 32-week CR rates and required a longer duration to achieve CR. These findings underscore the potential role of mixed dyslipidemia as an independent risk factor for slower responses to fertility-sparing treatment. The results suggest that metabolic factors such as mixed dyslipidemia, may impair treatment response. This is supported by our multivariable logistic regression analysis, which demonstrated that mixed dyslipidemia remained a statistically significant predictor of a lower 32-week CR rate even after adjusting for confounders, including age, BMI, MS, hypertension, diabetes, and progestin therapy. It may be important for clinicians to routinely screen for dyslipidemia in patients seeking fertility-preserving treatment and consider metabolic management as part of the treatment protocol.

The resistance to treatment in patients with mixed dyslipidemia may be mediated by underlying inflammatory pathways. Abnormal lipid metabolism often leads to elevated levels of multiple inflammatory factors, such as IL-1 $\beta$ , IL-6, IL-8, and TNF $\alpha$ , which contribute to the proliferation and angiogenesis of endometrium in the end [19, 20]. Patients with mixed dyslipidemia, who have multiple lipid abnormalities, may further aggravate the inflammatory state and lead to the insensitivity to progesterone treatment. Additionally, nearly half of the patients with dyslipidemia in our study were diagnosed IR, which can alter sex hormone binding globulin (SHBG) levels, which may increase circulating free estradiol

level[21]. IR may also enhance estrogen sensitivity in the endometrium by sensitizing estrogen receptors[22], and the inflammatory microenvironment induced by IR could further contribute to progestin resistance[23]. **Notably, a recent study demonstrated that a combination of ultrasonographic features and hysteroscopic findings could accurately predict endometrial malignancy and atypical hyperplasia through a structured prediction model[24]. This evidence suggests that endometrial structural and vascular characteristics detected by uterine cavity assessment may reflect underlying biological alterations. In this context, it is reasonable to hypothesize that similar imaging-based approaches, when integrated with metabolic parameters such as mixed dyslipidemia, may also help identify patients at increased risk of progestin insensitivity. Further investigation is needed to better understand the etiologic relationship between dyslipidemia and progestin insensitivity.**

Overweight has been widely accepted as a risk factor of CR in EEC and EAH patients. Our stratification analysis based on BMI and mixed dyslipidemia status provided further insights, demonstrating that overweight patients with mixed dyslipidemia had the lowest CR rates and longest treatment durations. This emphasizes the compounded adverse effects of overweight and mixed dyslipidemia, supporting the need for targeted metabolic interventions in this patient population. A previous study has indicated that weight loss improves response rates in women with obesity and EAH or EEC undergoing conservative management[25]. **Importantly, hysteroscopic guidance enables direct visualization and targeted removal of focal lesions, which may reduce residual disease burden and facilitate a more accurate and earlier confirmation of CR during follow-up, thereby improving overall treatment efficiency[2, 26]. Our results suggest that personalized treatment strategies, including addressing metabolic factors such as mixed dyslipidemia, and hysteroscopy-guided lesion control may improve treatment outcomes in this patient population. Clinicians could consider integrating lipid-lowering therapies, dietary interventions, and lifestyle modifications to optimize treatment response, particularly in patients**

with mixed dyslipidemia and those with overweight. Statins are a type of lipid-lowering drug used in clinics that lead to a reduction in cholesterol production. The use of statins has also been shown to improve survival of endometrial cancer patients[7]. However, there is no result of clinical study on statins in EAH and EEC patients seeking fertility preservation. These potential therapeutic mechanisms of statins may provide new insights for clinicians in treating EAH and EEC patients combined with mixed dyslipidemia.

To the best of our knowledge, this is the first study designed to investigate the effects of dyslipidemia and its components on the outcome of fertility-preserving treatment in EEC and EAH with a large sample size. Our major findings indicate that patients with mixed dyslipidemia exhibited significantly lower 32-week CR rates and required a longer duration to achieve CR, particularly those who were overweight. However, this study has several limitations. As a retrospective study, our findings are subject to inherent biases, such as selection bias and lacks randomization, which limits our ability to establish causal relationships. Our study was conducted at a single institution, which may limit the generalizability of the results to other populations or healthcare settings. The follow-up duration in our study was limited, with a median of 76.5 weeks, which allowed us to assess short-term treatment outcomes but may not fully capture long-term recurrence rates or fertility outcomes. A high-quality prospective, multi-center study is needed to clarify the effects of mixed dyslipidemia on fertility-sparing treatment in EAH and EEC patients.

## Reference

1. Rakha, E., et al., *Clinical outcome of atypical endometrial hyperplasia diagnosed on an endometrial biopsy: institutional experience and review of literature*. Am J Surg Pathol, 2012. **36**(11): p. 1683-90.
2. Vitale, S.G., et al., *Hysteroscopy in the management of endometrial*

- hyperplasia and cancer in reproductive aged women: new developments and current perspectives.* Transl Cancer Res, 2020. **9**(12): p. 7767-7777.
3. Liu, S., et al., *Effects of Weight Status and Related Metabolic Disorders on Fertility-Sparing Treatment Outcomes in Endometrial Atypical Hyperplasia and Endometrial Cancer: A Retrospective Study.* Cancers (Basel), 2022. **14**(20).
  4. Ciccone, M.A., et al., *Effectiveness of progestin-based therapy for morbidly obese women with complex atypical hyperplasia.* Arch Gynecol Obstet, 2019. **299**(3): p. 801-808.
  5. Yang, B., et al., *Insulin resistance and overweight prolonged fertility-sparing treatment duration in endometrial atypical hyperplasia patients.* J Gynecol Oncol, 2018. **29**(3): p. e35.
  6. Yang, X., et al., *Effects of Metabolic Syndrome and Its Components on the Prognosis of Endometrial Cancer.* Front Endocrinol (Lausanne), 2021. **12**: p. 780769.
  7. Lavie, O., et al., *The effect of statins on risk and survival of gynecological malignancies.* Gynecol Oncol, 2013. **130**(3): p. 615-9.
  8. Koh, W.J., et al., *Uterine Neoplasms, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology.* J Natl Compr Canc Netw, 2018. **16**(2): p. 170-199.
  9. Smith, K.B. and M.S. Smith, *Obesity Statistics.* Prim Care, 2016. **43**(1): p. 121-35, ix.

10. *2016 Chinese guideline for the management of dyslipidemia in adults.* Zhonghua Xin Xue Guan Bing Za Zhi, 2016. **44**(10): p. 833-853.
11. Paquette, M., et al., *Prevalence of Dysbetalipoproteinemia in the UK Biobank According to Different Diagnostic Criteria.* J Clin Endocrinol Metab, 2024.
12. Matthews, D.R., et al., *Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man.* Diabetologia, 1985. **28**(7): p. 412-9.
13. Shan, W., et al., *Hyperinsulinemia is associated with endometrial hyperplasia and disordered proliferative endometrium: a prospective cross-sectional study.* Gynecol Oncol, 2014. **132**(3): p. 606-10.
14. Trabert, B., et al., *Metabolic syndrome and risk of endometrial cancer in the united states: a study in the SEER-medicare linked database.* Cancer Epidemiol Biomarkers Prev, 2015. **24**(1): p. 261-7.
15. Hanson, R.L., et al., *Components of the "metabolic syndrome" and incidence of type 2 diabetes.* Diabetes, 2002. **51**(10): p. 3120-7.
16. Klein, B.E., R. Klein, and K.E. Lee, *Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in Beaver Dam.* Diabetes Care, 2002. **25**(10): p. 1790-4.
17. Li, X., et al., *Insulin Resistance and Metabolic Syndrome Increase the Risk of Relapse For Fertility Preserving Treatment in Atypical Endometrial Hyperplasia and Early Endometrial Cancer Patients.* Front

- Oncol, 2021. **11**: p. 744689.
18. Ding, Y., et al., *Metabolic syndrome is an independent risk factor for time to complete remission of fertility-sparing treatment in atypical endometrial hyperplasia and early endometrial carcinoma patients.* Reprod Biol Endocrinol, 2022. **20**(1): p. 134.
19. Hefetz-Sela, S. and P.E. Scherer, *Adipocytes: impact on tumor growth and potential sites for therapeutic intervention.* Pharmacol Ther, 2013. **138**(2): p. 197-210.
20. Dossus, L., et al., *Tumor necrosis factor (TNF)-alpha, soluble TNF receptors and endometrial cancer risk: the EPIC study.* Int J Cancer, 2011. **129**(8): p. 2032-7.
21. Simo, R., et al., *Novel insights in SHBG regulation and clinical implications.* Trends Endocrinol Metab, 2015. **26**(7): p. 376-83.
22. Lv, Q.Y., et al., *Increased TET1 Expression in Inflammatory Microenvironment of Hyperinsulinemia Enhances the Response of Endometrial Cancer to Estrogen by Epigenetic Modulation of GPER.* J Cancer, 2017. **8**(5): p. 894-902.
23. Patel, B.G., et al., *Progesterone resistance in endometriosis: origins, consequences and interventions.* Acta Obstet Gynecol Scand, 2017. **96**(6): p. 623-632.
24. Vitale, S.G., et al., *Risk of endometrial malignancy in women treated for breast cancer: the BLUSH prediction model - evidence from a*

- comprehensive multicentric retrospective cohort study*. *Climacteric*, 2024. **27**(5): p. 482-488.
25. Barr, C.E., et al., *Weight Loss During Intrauterine Progestin Treatment for Obesity-associated Atypical Hyperplasia and Early-Stage Cancer of The Endometrium*. *Cancer Prev Res (Phila)*, 2021. **14**(11): p. 1041-1050.
26. Kuribayashi, Y., et al., *Frequency of endometrial cancer and atypical hyperplasia in infertile women undergoing hysteroscopic polypectomy*. *J Obstet Gynaecol Res*, 2017. **43**(9): p. 1465-1471.

### **Acknowledgments**

We thank all the patients who participated in this study.

### **Author Contributions**

All authors contributed to the study conception and design. Data collection was performed by Shuhan Luo, Manrong Wang, Qujia Gama and Lulu Wang. Data analysis was performed by Shuhan Luo, Pengfei Wu and Sijia Liu. The first draft of the manuscript was written by Shuhan Luo and Pengfei Wu. The manuscript was edited by Xuezheng Luo and Pengfei Wu.

### **Competing interests**

The authors declare no competing interests.

### **Data availability**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### **Ethics declarations**

The retrospective study was approved by the Ethics Committee of the Obstetrics and Gynecology Hospital of Fudan University (No. 2022-203).

### **Funding Statement**

This work was funded by the National Key R&D Program of China (Grant No. 2022YFC2704301 and 2022YFC2704305), Medical Engineering Joint Fund of Fudan University (Grant No. yg2023-08), and Shanghai Anticancer Association EYAS PROJECT (Grant No. SACA-CY22C08), and The Shanghai Municipal Health Commission Youth Program (Grant No. 20224Y0084).

### **Figure 1 Legend**

#### **Flowchart of our study.**

EAH, endometrial atypical hyperplasia; EEC, endometrioid endometrial cancer.

### **Figure 2 Legend**

#### **Cumulative CR rate in patients with and without dyslipidemia.**

CR, complete response; 95% CI, 95% confidence interval; HR, hazard ratio.

### **Figure 3 Legend**

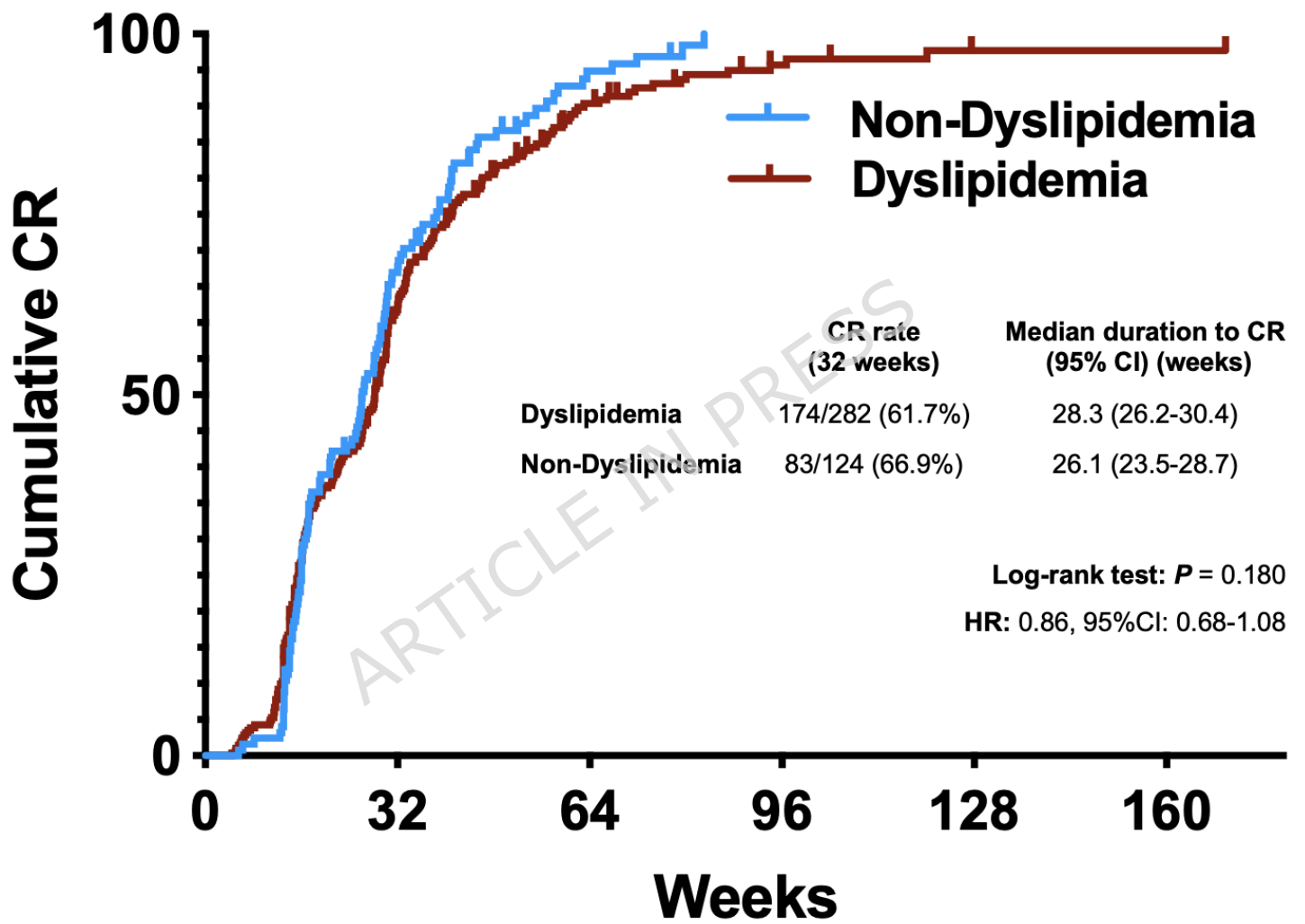
#### **Cumulative CR rate in patients with and without mixed dyslipidemia.**

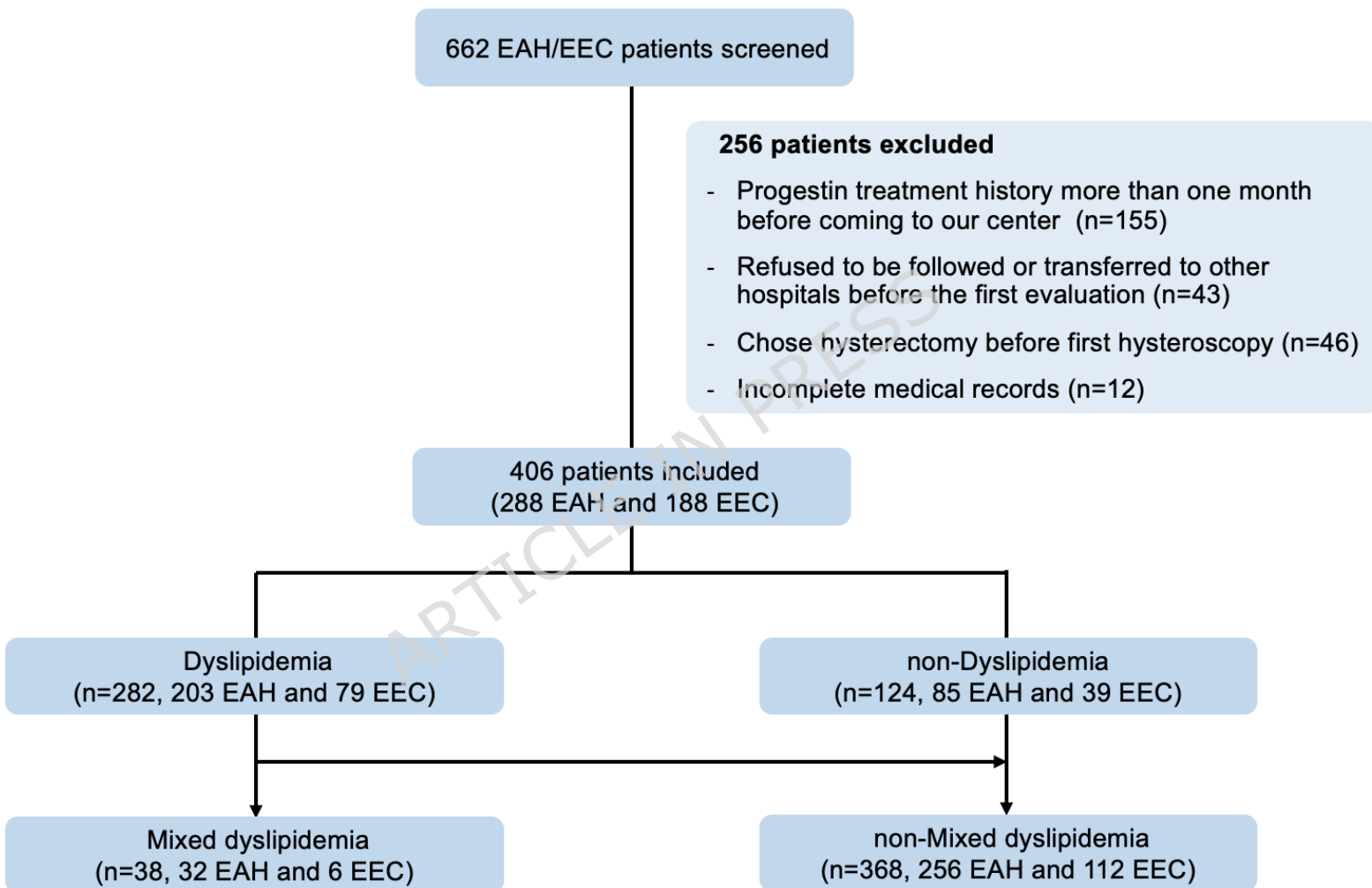
NMD, non-mixed dyslipidemia; MD, mixed dyslipidemia; CR, complete response; 95% CI, 95% confidence interval; HR, hazard ratio.

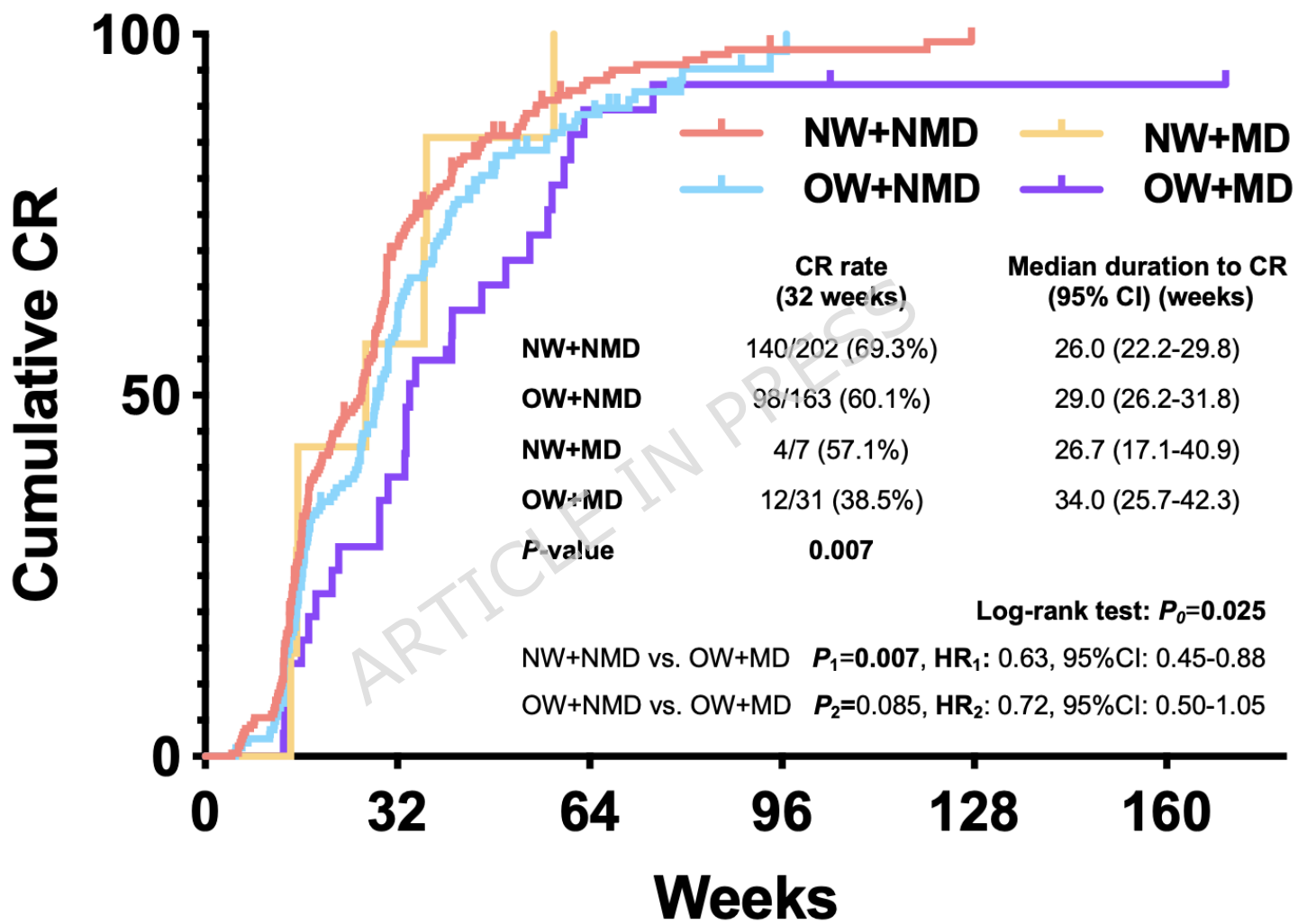
### **Figure 4 Legend**

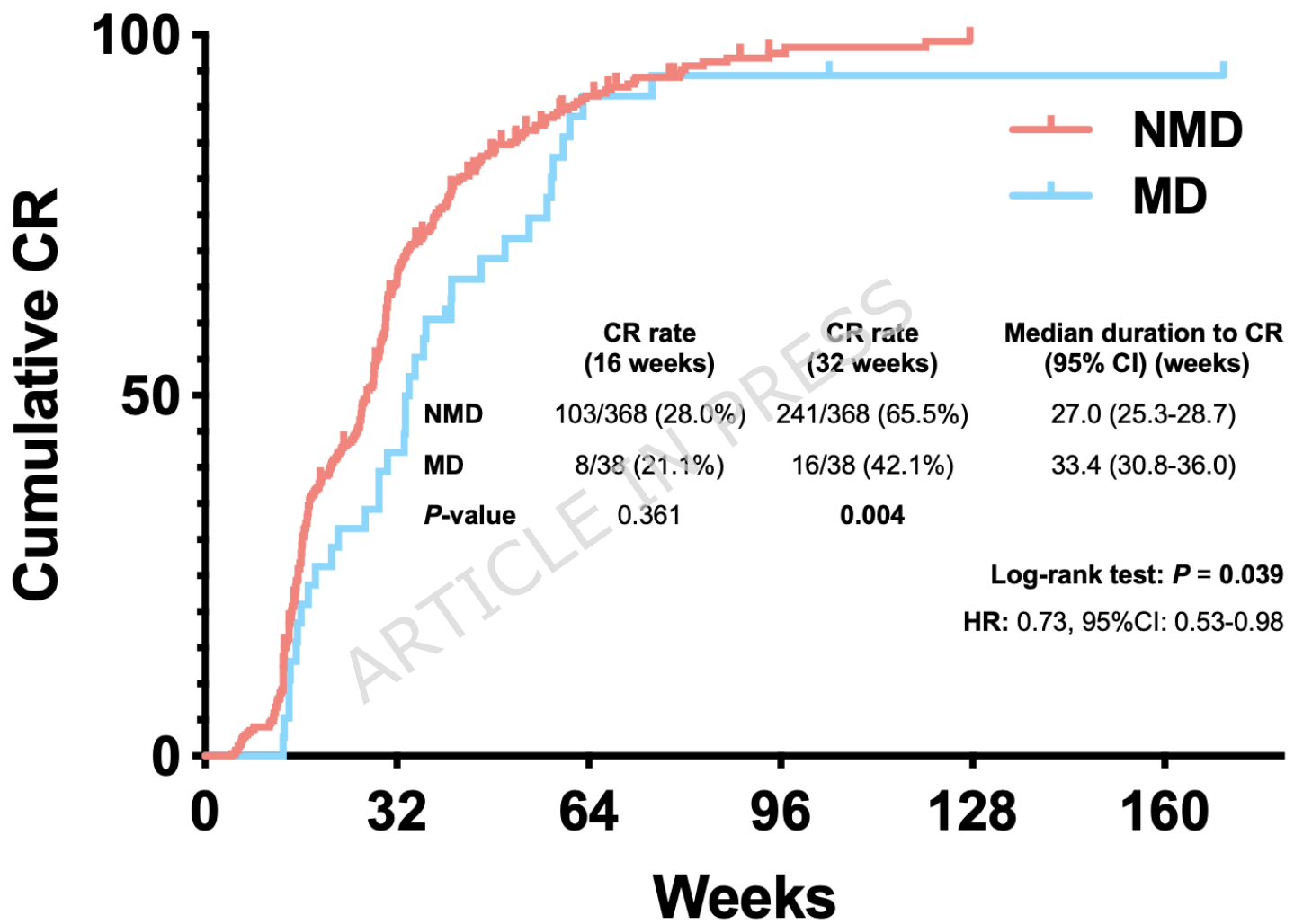
#### **Cumulative CR rate in patients with and without mixed dyslipidemia stratified by BMI.**

NW, normal weight; NMD, non-mixed dyslipidemia; OW, overweight; MD, mixed dyslipidemia; CR, complete response; 95% CI, 95% confidence interval; HR, hazard ratio; BMI, body mass index.









**Table 1. General characteristics of study population.**

	Dyslipidemia		Total	P-value
	YES	NO		
<b>No. of patients, n (%)</b>	282(69.5%)	124(30.5%)	406	-
<b>Age at diagnosis (yr)</b>	32	31	32	0.819
<b>Median (range)</b>	(18-44)	(19-45)	(18-45)	
<b>BMI (kg/m<sup>2</sup>)</b>	24.97	23.62	24.89	0.184
<b>Median (range)</b>	(16.73-47.48)	(16.38-51.56)	(16.38-51.56)	
<b>IR, n (%)</b>	121(42.9)	38(30.6)	159(39.2)	<b>0.020</b>
<b>MS, n (%)</b>	114(40.4)	30(24.2)	144(35.5)	<b>0.002</b>
<b>Hypertension, n (%)</b>	69(24.5)	28(22.6)	97(23.9)	0.681
<b>Diabetes mellitus, n (%)</b>	35(12.4)	7(5.6)	42(10.3)	<b>0.039</b>
<b>Pathological diagnosis, n (%)</b>	□	□	□	0.482
<b>EAH</b>	203(72.0)	85(68.5)	288(70.9)	-□
<b>EEC</b>	79(28.0)	39(31.5)	188(29.1)	-□
<b>Progestin therapy, n (%)</b>				0.060
<b>MA</b>	117(41.5)	41(33.1)	158(38.9)	-
<b>MA+MET</b>	51(18.1)	34(27.4)	85(20.9)	-
<b>LNG-IUS</b>	56(19.9)	22(17.7)	78(19.2)	-
<b>MA+LNG-IUS</b>	11(3.9)	1(0.8)	12(3.0)	-
<b>MA+LNG-IUS+MET</b>	47(16.7)	26(21.0)	73(18.0)	-

Footnote□

BMI, body mass index; IR, insulin resistant; MS, metabolic syndrome; EAH, endometrial atypical hyperplasia; EEC, endometrioid endometrial cancer; MA, megestrol acetate; MET, metformin; LNG-IUS, levonorgestrel intrauterine system. P-value: Comparison between Dyslipidemia and non-Dyslipidemia group. The bold values denote statistical significance at  $P < 0.05$  level.

**Table 3. Uni- and multivariate analyses of factors associated with 32-week CR.**

	32-week CR N=257	Crude model <sup>a</sup>		Model 1 <sup>b</sup>		Model 2 <sup>c</sup>		Model 3 <sup>d</sup>	
		OR (95% CI)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value
<b>Pathological diagnosis, n (%)</b>									
EAH	192(66.7)	1		1		1		1	
EEC	65(34.6)	0.613 (0.396-0.950)	<b>0.029</b>	0.580 (0.369-0.913)	<b>0.018</b>	0.608 (0.383-0.965)	<b>0.035</b>	0.607 (0.382-0.963)	<b>0.034</b>
<b>Overweight, n (%)</b>									
NO	147(69.3)	1		1		1		1	
YES	110(56.7)	0.591 (0.393-0.889)	<b>0.012</b>	0.655 (0.429-0.999)	0.050	0.589 (0.351-0.990)	<b>0.046</b>	0.589 (0.351-0.991)	<b>0.046</b>
<b>Mixed dyslipidemia, n (%)</b>									
NO	241(65.5)	1		1		1		1	
YES	16(42.1)	0.383 (0.194-0.756)	<b>0.006</b>	0.408 (0.201-0.826)	<b>0.013</b>	0.320 (0.133-0.769)	<b>0.011</b>	0.322 (0.134-0.775)	<b>0.011</b>

## Footnote□

CR, complete response; OR, odds ratio; CI, confidence interval; EAH, endometrial atypical hyperplasia; EEC, endometrioid endometrial cancer; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Apo A, apolipoprotein A; IR, insulin resistance; MS, metabolic syndrome; DM, diabetes mellitus.

<sup>a</sup> Unadjusted covariates. We analyzed the covariates including age at diagnosis, overweight, pathological diagnosis, TC, TG, HDL, LDL, Apo A, mixed dyslipidemia, IR, MS, hypertension, DM, and progestin therapy, and only showed the significant result. <sup>b</sup> Adjusted for age at diagnosis, overweight, pathological diagnosis, mixed dyslipidemia. <sup>c</sup> Adjusted for age at diagnosis, overweight, pathological diagnosis, mixed dyslipidemia, HDL, LDL, IR, MS, hypertension, DM. <sup>d</sup> Adjusted for age at diagnosis, overweight, pathological diagnosis, mixed dyslipidemia, HDL, LDL, IR, MS, hypertension, DM, progestin therapy. The bold values denote statistical significance at  $P < 0.05$  level.

**Table 2. Treatment outcomes in dyslipidemia and non-dyslipidemia patients.**

	Dyslipidemia		Total	P-value
	YES	NO		
<b>No. of patients</b>	282	124	406	-
<b>16-week CR rate, n (%)</b>	76(27.0)	35(28.2)	111(27.3)	0.810
<b>EAH</b>	57(28.1)	29(34.1)	86(29.9)	0.325
<b>EEC</b>	19(24.1)	6(15.4)	25(21.2)	0.343
<b>32-week CR rate, n (%)</b>	174(61.7)	83(66.9)	257(63.3)	0.371
<b>EAH</b>	132(65.0)	60(70.6)	192(66.7)	0.412
<b>EEC</b>	42(59.0)	23(53.2)	65(55.1)	0.563
<b>Treatment duration to CR (weeks) Median (95% CI)</b>	28.3 (26.2-30.4)	26.1 (23.5-28.7)	28.0 (26.5-29.5)	0.180
<b>EAH</b>	27.0(23.9-30.1)	20.9(14.0-27.7)	25.9(22.8-28.9)	0.186
<b>EEC</b>	30.4(27.4-33.5)	29.7(26.3-33.1)	30.1(28.0-32.3)	0.530
<b>Pregnant rate*, n (%)</b>	41/90(45.6)	18/44(40.9)	59/134(44.0)	0.611
<b>EAH</b>	29/59(49.2)	12/28(42.9)	41/87(47.1)	0.583
<b>EEC</b>	12/31(38.7)	6/16(37.5)	18/47(38.3)	0.936
<b>Live birth rate§, n (%)</b>	27/41(65.9)	9/18(50.0)	36/59(61.0)	0.376
<b>EAH</b>	19/29(65.5)	7/12(58.3)	26/41(63.4)	0.603
<b>EEC</b>	8/12(66.7)	2/6(33.3)	10/18(55.6)	0.501
<b>Recurrent rate†, n (%)</b>	21/255(8.2)	6/117(5.1)	27/372(7.3)	0.283
<b>EAH</b>	13/181(7.2)	4/82(4.9)	17/263(6.5)	0.481
<b>EEC</b>	8/74(10.8)	2/35(5.7)	10/109(9.2)	0.496

Footnote□

CR, complete response; EAH, endometrial atypical hyperplasia; EEC, endometrioid endometrial cancer; CI, confidence interval.

\*Among patients who attempted pregnancy after achieving CR. §Among patients who achieved pregnancy. †Among patients who achieved CR.

P-value: Comparison between Dyslipidemia and non-Dyslipidemia group. The bold values denote statistical significance at  $P < 0.05$  level.