

Pregnancy Outcomes Following Medical Therapy versus Levonorgestrel-Releasing Intrauterine System for Atypical Endometrial Hyperplasia

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Objective: To compare pregnancy outcomes between systemic progestin therapy and levonorgestrel-releasing intrauterine system (LNG-IUS) in patients with atypical endometrial hyperplasia (AEH) desiring fertility preservation.

Methods: This single-center retrospective cohort study included AEH patients who underwent fertility-sparing treatment between January 2017 and December 2024. Patients received either systemic progestins (medroxyprogesterone acetate [MPA] 250–600 mg/day, megestrol acetate [MA] 160–320 mg/day, or dydrogesterone 20–40 mg/day) or LNG-IUS. Primary outcomes were clinical pregnancy rate and live birth rate. Secondary outcomes included time to pregnancy (TTP), conception mode, and disease recurrence rate. Propensity score matching (PSM) controlled for confounders including age, body mass index, polycystic ovary syndrome, and infertility duration.

Results: Of 186 patients (121 medical therapy, 65 LNG-IUS), 58 per group were analyzed after PSM. Complete remission rates were 77.6% (45/58) versus 84.5% (49/58) (adjusted OR 1.52, 95% CI 0.71–3.26, $p=0.28$). Among patients achieving complete remission, clinical pregnancy rates were 51.1% (23/45) versus 67.3% (33/49) (adjusted OR 2.14, 95% CI 1.08–4.25, $p=0.029$). Live birth rates were 37.8% (17/45) versus 55.1% (27/49) (adjusted OR 2.28, 95% CI 1.13–4.62, $p=0.022$). Median TTP was 8.5 months (IQR 6–14) versus 6.0 months (IQR 4–10) (HR 1.64, 95% CI 1.12–2.41, $p=0.011$). Per-protocol analysis yielded consistent results.

Conclusion: LNG-IUS treatment was associated with significantly higher clinical pregnancy rates, live birth rates, and shorter TTP compared to systemic progestin therapy. These findings support LNG-IUS as a preferred fertility-sparing option for AEH patients, particularly when expedited conception is desired. Results should be interpreted considering the retrospective design, heterogeneous dosing, and potential residual confounding.

Keywords: atypical endometrial hyperplasia, levonorgestrel-releasing intrauterine system, fertility preservation, pregnancy outcomes, retrospective cohort

Introduction

Atypical endometrial hyperplasia (AEH) represents a precancerous condition with significant malignant potential, characterized by architectural complexity and cytological atypia of endometrial glands.^{1,2} The updated World Health Organization classification system designates AEH as endometrial intraepithelial neoplasia (EIN), reflecting its premalignant nature with an estimated annual progression rate to endometrial carcinoma of approximately 8%.³ For women of reproductive age with fertility preservation desires, this diagnosis presents a clinical dilemma between definitive surgical treatment and conservative management strategies.

The standard treatment for AEH remains total hysterectomy with bilateral salpingo-oophorectomy, which eliminates malignant potential but precludes future fertility.⁴ However, an increasing proportion of women are delaying child-bearing, and approximately 10–15% of endometrial cancer cases occur in premenopausal women.⁵ This demographic

shift has driven development of fertility-sparing approaches, primarily utilizing high-dose progestin therapy to reverse endometrial proliferation and induce regression of atypical lesions. Importantly, the present study focused exclusively on AEH without including Grade 1 (G1) endometrioid carcinoma. Although G1 endometrial cancer without myometrial invasion is also considered a standard indication for fertility-sparing treatment, we restricted enrollment to AEH because the biological behavior, recurrence patterns, and therapeutic response profiles of AEH and early endometrial carcinoma differ meaningfully.^{6,7} Including G1 carcinoma cases would introduce significant clinical heterogeneity, potentially confounding the comparison of treatment modalities for a single disease entity. Furthermore, distinct treatment escalation pathways and surveillance requirements for carcinoma versus hyperplasia justified separate investigation.

Systemic progestin therapy, including medroxyprogesterone acetate (MPA), megestrol acetate (MA), and dydrogesterone, has demonstrated efficacy in achieving disease regression with reported complete response rates ranging from 68% to 87%.^{8,9} A systematic review by Gallos et al reported pooled pregnancy rates of approximately 34% and live birth rates of 25% among women who achieved remission following oral progestin therapy for AEH.¹⁰ Similarly, Park et al documented pregnancy rates of 36.7% after MPA-based fertility-sparing treatment.¹¹ These agents exert antiproliferative effects through progesterone receptor-mediated pathways, inducing endometrial decidualization and suppressing estrogen-driven hyperplasia.¹² However, systemic administration is associated with notable adverse effects including weight gain, mood disturbances, thromboembolic risk, and metabolic alterations that may compromise treatment adherence and long-term outcomes.^{13,14}

The levonorgestrel-releasing intrauterine system (LNG-IUS) has emerged as an alternative fertility-sparing strategy, delivering high local concentrations of progestin directly to the endometrium while minimizing systemic exposure.¹⁵ The 52 mg LNG-IUS achieves daily intrauterine levonorgestrel release of approximately 20 µg, producing potent local antiproliferative effects with substantially lower systemic hormone levels compared to oral formulations.¹⁶ Systematic reviews and meta-analyses have reported complete response rates of 79–87% with LNG-IUS treatment, with lower relapse rates (11–14%) compared to oral progestins (28–33%).^{10,17} In terms of pregnancy outcomes specifically, De Rocco et al reported pooled pregnancy rates of approximately 42% and live birth rates of 32% following LNG-IUS-based fertility-sparing approaches.¹⁷ Despite these individual modality data, direct comparisons of pregnancy outcomes between LNG-IUS and systemic progestins within a single cohort remain scarce, and most existing evidence is limited to comparisons of oncologic response rather than reproductive endpoints.

Despite accumulating evidence supporting both therapeutic modalities, comparative data on reproductive outcomes remain limited. Several observational studies have examined pregnancy rates following fertility-sparing treatment, with live birth rates ranging from 20–48% across different treatment protocols.^{10,18} Factors including polycystic ovary syndrome (PCOS), obesity, insulin resistance, and prolonged treatment duration may influence both oncologic and reproductive outcomes.^{19,20} Additionally, the utilization of assisted reproductive technology (ART) has been associated with higher live birth rates (39.4%) compared to spontaneous conception attempts (14.9%) in this population.²¹

Current evidence gaps include the relative efficacy of LNG-IUS versus systemic progestins for achieving pregnancy, optimal timing for conception attempts following disease remission, and identification of predictive factors for successful fertility preservation. The role of adjuvant therapies such as metformin, particularly in patients with metabolic dysfunction or PCOS, requires further investigation.^{19,22} Furthermore, long-term disease recurrence risks following pregnancy and strategies for postpartum surveillance remain incompletely defined.²³

We hypothesized that in a real-world patient population, LNG-IUS treatment would be associated with higher clinical pregnancy and live birth rates, or shorter time to pregnancy, compared to systemic progestin therapy. This retrospective cohort study aimed to: (1) compare pregnancy outcomes between medical therapy and LNG-IUS treatment groups; (2) evaluate disease response and recurrence patterns; (3) identify predictive factors for successful fertility preservation; and (4) characterize the role of ART in this clinical context. Understanding these comparative outcomes will inform evidence-based counseling and treatment selection for women with AEH desiring fertility preservation.

Materials and Methods

Study Design and Ethics Approval

This single-center retrospective cohort study was conducted at the Reproductive Medicine/Gynecology Center. We retrieved data from the electronic medical record (EMR) system, pathology database, and follow-up registries to identify patients with AEH who received fertility-sparing treatment between January 2017 and December 2024. The study protocol received approval from Wuxi Maternity and Child Health Care Hospital Ethics Committee (Approval Number: IEC-FOM-17015). This study was conducted in compliance with the Declaration of Helsinki. All patients signed informed consent forms. All data were de-identified in accordance with privacy regulations. No additional interventions beyond standard clinical care were performed.

Study Population and Selection Criteria

Eligible participants were identified through systematic database queries using International Classification of Diseases codes and pathology records. Inclusion criteria comprised: (1) histopathologically confirmed atypical endometrial hyperplasia based on diagnostic curettage or hysteroscopic biopsy, reviewed by experienced gynecologic pathologists according to 2014 WHO classification criteria; (2) documented desire for fertility preservation with explicit informed consent for conservative management; (3) receipt of initial treatment with either systemic progestin therapy (medical therapy group) or LNG-IUS placement (LNG-IUS group); and (4) availability of complete treatment records and reproductive outcome follow-up data, including at least one of the following endpoints: conception, pregnancy termination, or treatment outcome determination. Exclusion criteria encompassed: (1) concurrent diagnosis of endometrial carcinoma at baseline evaluation or during treatment course, confirmed by comprehensive pathology review and imaging assessment; (2) coexisting severe medical conditions requiring priority oncologic treatment that would preclude conservative management; (3) prior endometrial ablation or extensive uterine cavity procedures resulting in non-assessable endometrium; (4) missing critical outcome variables or core covariates that could not be imputed using established statistical methods; and (5) concurrent initiation of both LNG-IUS and systemic progestin therapy without clear primary treatment modality, which would confound exposure classification. Patients meeting exclusion criteria were documented with specific reasons for non-inclusion.

Exposure Definition and Group Assignment

The medical therapy group comprised patients whose initial fertility-sparing treatment consisted primarily of systemic progestin administration, including medroxyprogesterone acetate (MPA) at doses of 250–600 mg daily, megestrol acetate (MA) at 160–320 mg daily, or dydrogesterone at 20–40 mg daily. Specific dosing regimens, treatment duration, and any protocol modifications were systematically recorded. We acknowledge that the lower end of MPA dosing (250 mg/day) falls below the standard high-dose regimens (400–600 mg/day) typically recommended in oncologic guidelines. This dosage variability reflects real-world clinical practice where treating physicians adjusted doses based on individual patient tolerability, body weight, and metabolic comorbidities. The impact of this heterogeneity on outcomes is addressed in the sensitivity analyses and limitations. The LNG-IUS group included patients who underwent placement of the 52 mg levonorgestrel-releasing intrauterine system (Mirena®) as initial treatment, typically performed under ultrasound or hysteroscopic guidance to ensure optimal fundal positioning.

Treatment crossover events, defined as patients initially receiving one modality who subsequently switched to the alternative approach due to inadequate response, intolerable adverse effects, or patient preference, were documented and handled according to intention-to-treat principles for primary analyses. Patients were categorized based on their initial treatment assignment regardless of subsequent crossover. Sensitivity analyses were conducted to evaluate per-protocol effects, restricted to patients who completed their assigned treatment without crossover, and to assess the impact of treatment switching on outcome interpretation.

Follow-Up Protocol and Endometrial Surveillance

Following treatment initiation, patients underwent endometrial sampling via office endometrial biopsy or diagnostic hysteroscopy with curettage at 3-month intervals for the first 12 months, and every 6 months thereafter until complete remission was achieved. After documented CR, endometrial surveillance continued with sampling every 6 months during the conception attempt period. These standardized surveillance intervals provided the basis for calculating time to complete remission.

Definitions of Recurrence and Criteria for Hysterectomy

Disease recurrence was defined as histopathologic re-documentation of AEH or endometrial carcinoma on endometrial biopsy following a previously confirmed complete remission. Pre-conception recurrence was defined as recurrence occurring before any pregnancy attempt, while postpartum recurrence was defined as recurrence detected during scheduled surveillance after delivery. Criteria for recommending hysterectomy in refractory cases included: (1) failure to achieve at least partial response after 12 months of adequate progestin therapy; (2) histologic progression to endometrial carcinoma at any time during conservative management; (3) disease recurrence after a second course of progestin-based treatment; or (4) patient request for definitive surgery following adequate counseling.

Maintenance Therapy and Permission to Conceive

Following achievement of CR, patients in the medical therapy group received maintenance progestin therapy at reduced doses (MPA 250 mg/day or MA 160 mg/day) for an additional 2–3 months, after which treatment was discontinued and patients were counseled to attempt conception immediately. Patients in the LNG-IUS group had the device removed upon confirmation of CR, and were similarly advised to pursue conception without delay. In both groups, conception attempts were recommended within 3–6 months of confirmed CR to minimize the risk of recurrence during the pre-conception window.

Assisted Reproductive Technology Protocols

Among patients utilizing ART, ovarian stimulation was performed using standard protocols at our institution. Controlled ovarian hyperstimulation employed gonadotropin-releasing hormone (GnRH) antagonist protocols in the majority of cases (72%), with recombinant follicle-stimulating hormone (rFSH, Gonal-F; starting dose 150–300 IU/day adjusted by ovarian response) as the primary stimulation agent. GnRH agonist long protocols were used in the remaining 28% of cases. Ovulation triggering was achieved with recombinant human chorionic gonadotropin (rHCG, 250 µg) or dual trigger (GnRH agonist plus low-dose HCG) in patients at high risk for ovarian hyperstimulation syndrome. Intrauterine insemination (IUI) was performed 36 hours after trigger injection, while oocyte retrieval for IVF/ICSI was performed 34–36 hours after trigger. Luteal phase support consisted of vaginal progesterone (Utrogestan, 200 mg three times daily) initiated on the day of embryo transfer and continued until 10 weeks of gestation if pregnancy was achieved.

Outcome Measures

Primary Outcomes: The co-primary endpoints were (1) clinical pregnancy rate, defined as ultrasonographic visualization of an intrauterine gestational sac with fetal cardiac activity at 6–8 weeks gestation, and (2) live birth rate, defined as delivery of a viable infant at ≥ 24 weeks gestation. These endpoints were selected based on their clinical relevance and consistency with prior fertility preservation literature. **Secondary Outcomes:** Time to pregnancy (TTP) was calculated from the date of documented complete remission (CR) to clinical pregnancy confirmation, with alternative calculation from treatment initiation for patients who conceived prior to formal CR documentation. Mode of conception was categorized as spontaneous conception (natural intercourse without medical intervention) versus ART-assisted conception, with ART encompassing ovulation induction, intrauterine insemination, in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI). Pregnancy loss outcomes included first-trimester miscarriage (< 12 weeks), second-trimester loss (12–24 weeks), and third-trimester stillbirth (≥ 24 weeks). Disease recurrence was defined as histopathologic documentation of AEH or endometrial carcinoma following previous CR, categorized temporally as pre-conception recurrence (occurring before pregnancy attempt) or postpartum recurrence (detected after delivery). Pathologic response

was classified as complete remission (CR, absence of hyperplasia with normal endometrial histology), partial response (PR, improvement without complete resolution), or no response (NR, persistent AEH). Time to CR was measured from treatment initiation to pathologic confirmation of remission. Treatment-related adverse events were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Covariate Assessment and Potential Confounders

Comprehensive baseline characteristics were systematically extracted from medical records to identify potential confounding variables and enable propensity score development. Demographic variables included age at AEH diagnosis (years), body mass index (BMI, kg/m²), and race/ethnicity. Reproductive history encompassed parity, gravidity, documented infertility duration (years of regular unprotected intercourse without conception), and prior pregnancy outcomes. Menstrual patterns were categorized as regular (cycle interval 21–35 days), oligomenorrhea (cycle interval >35 days), or amenorrhea (absence of menses for ≥3 months). Clinical comorbidities of interest included polycystic ovary syndrome (PCOS) diagnosed according to Rotterdam criteria (≥2 of: hyperandrogenism, oligo/anovulation, polycystic ovarian morphology), type 2 diabetes mellitus, hypertension, and dyslipidemia. Metabolic parameters measured at baseline included fasting glucose, fasting insulin, homeostatic model assessment of insulin resistance (HOMA-IR, calculated as fasting glucose × fasting insulin / 405), hemoglobin A1c, and lipid profile (total cholesterol, LDL, HDL, triglycerides). Baseline endometrial assessment included transvaginal ultrasound measurement of endometrial thickness (mm), magnetic resonance imaging (MRI) evaluation when performed, and hysteroscopic findings documenting lesion distribution (focal versus diffuse), presence of endometrial polyps, and any structural abnormalities.

Disease characteristics recorded from pathology reports included extent of endometrial involvement, presence of concurrent simple or complex hyperplasia without atypia, and any concerning architectural features. Previous uterine procedures were documented, including dilation and curettage (D&C), hysteroscopic polypectomy, myomectomy, and cesarean delivery. Lifestyle factors and additional medical conditions recorded when available included smoking status (never, former, current), alcohol consumption, and chronic medication use (particularly metformin in PCOS patients). The interval from diagnostic biopsy to treatment initiation was calculated to assess potential impact of diagnostic-to-treatment delay on outcomes. Additionally, liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin) were monitored at baseline and every 3 months during oral progestin therapy, as hepatic monitoring is standard practice for patients receiving high-dose systemic progestins.

Data Sources and Quality Control

All study variables were extracted from multiple integrated data sources to ensure comprehensive and accurate information capture. The primary EMR system provided demographic data, clinical notes, laboratory results, medication records, and imaging reports. The institutional pathology database contained detailed histopathologic diagnoses, specimen descriptions, immunohistochemistry results, and pathologist interpretations. Follow-up data were obtained from outpatient clinic visits, telephone contacts, and coordination with referring providers when patients received pregnancy care at external facilities.

A rigorous quality control process was implemented to maximize data reliability. Two independent research coordinators performed parallel data extraction using standardized case report forms with explicit variable definitions and coding instructions. A third senior investigator adjudicated all discrepancies identified during initial extraction, reviewing source documents to resolve inconsistencies. For critical endpoint variables (clinical pregnancy, live birth, miscarriage, disease recurrence), dual verification was mandated requiring concordant documentation in at least two independent data sources (eg, ultrasound report plus clinical note, pathology report plus follow-up record, delivery record plus neonatal documentation).

Missing data patterns were systematically characterized, with missingness mechanisms classified as missing completely at random (MCAR), missing at random (MAR), or not missing at random (NMAR) based on statistical testing and clinical judgment. For variables with missing rates <20%, multiple imputation with chained equations (MICE) was employed using $m=20$ imputations, incorporating all covariates and outcome variables in the imputation models. Variables with missingness >20% were flagged, and sensitivity analyses excluded these variables to assess robustness.

of findings. Extreme values and potential data entry errors were identified through range checks and logical consistency algorithms, with queries generated for source document verification.

Statistical Analysis

Descriptive statistics were calculated with continuous variables presented as mean $\pm$ SD or median [IQR] based on normality testing, and categorical variables as frequencies and percentages. Group comparisons utilized chi-square/Fisher's exact tests for categorical variables and *t*-tests/Mann–Whitney *U*-tests for continuous variables. Propensity score matching was performed using multivariable logistic regression including age, BMI, infertility duration, PCOS status, metabolic parameters, and disease characteristics, achieving good discrimination (C-statistic 0.72) and excellent covariate balance (all SMD <0.1). Primary outcomes were analyzed using multivariable logistic regression for clinical pregnancy and live birth (adjusted OR with 95% CI), and Cox proportional hazards regression for time-to-pregnancy (HR with 95% CI). Disease response and recurrence analyses employed competing risks methodology using Fine-Gray regression to account for pregnancy/live birth as competing events. Comprehensive sensitivity analyses and pre-specified subgroup analyses examined treatment effect heterogeneity across clinically relevant strata including age, BMI, PCOS status, and conception method. A per-protocol analysis was conducted excluding patients who crossed over between treatment groups (18 patients from the medical therapy group and 7 from the LNG-IUS group) to assess the robustness of the intention-to-treat findings and estimate pure treatment effects. Additionally, sensitivity analyses stratified the medical therapy group by progestin dose (MPA ≥ 400 mg/day vs. <400 mg/day) to evaluate whether dosage heterogeneity influenced outcomes. Multiple hypothesis testing correction used the Benjamini-Hochberg FDR procedure (threshold 0.05), with two-sided tests at $\alpha=0.05$. All analyses were performed using R version 4.2.0 with packages including MatchIt, survival, cmprsk, and mice.

Results

Patient Selection and Baseline Characteristics

During the study period, 253 patients with suspected endometrial hyperplasia underwent diagnostic evaluation at our institution. Following systematic screening, 186 patients met inclusion criteria for analysis, while 67 patients were excluded for the following reasons: pathology review revealing diagnoses other than AEH ($n=23$), absence of adequate follow-up data ($n=18$), unclear or undocumented treatment pathway ($n=12$), suspected or confirmed endometrial cancer during initial workup ($n=9$), and critical missing data that could not be reliably imputed ($n=5$). The detailed patient selection process is depicted in [Figure 1](#), which follows CONSORT-style reporting guidelines adapted for observational studies.

The final unmatched cohort comprised 121 patients in the medical therapy group and 65 patients in the LNG-IUS group. In the unmatched cohort, the LNG-IUS group was significantly younger (30.8 ± 4.2 vs. 32.4 ± 4.8 years, $p=0.021$), had lower BMI (25.9 ± 4.6 vs. 27.8 ± 5.2 kg/m², $p=0.012$), and showed a trend toward shorter infertility duration (median 2.0 vs. 2.5 years, $p=0.067$), suggesting that clinicians may have preferentially selected patients with more favorable baseline profiles for LNG-IUS treatment. After propensity score matching using 1:1 nearest neighbor matching with caliper 0.2, 58 patients per group were successfully matched and included in the primary analysis ([Figure 2](#)). Post-matching, all standardized mean differences were <0.1 , indicating excellent covariate balance between groups. The median follow-up duration was 36.2 months (IQR 24.5–48.8) for the medical therapy group and 34.8 months (IQR 22.6–46.5) for the LNG-IUS group. Baseline characteristics for both unmatched and PSM cohorts are summarized in [Table 1](#).

Treatment Pathways and Disease Response

Treatment regimens and pathologic response patterns are detailed in [Table 2](#) and [Figure 3](#). In the medical therapy group, the most commonly prescribed systemic progestin was medroxyprogesterone acetate (MPA) at 400–600 mg daily (72 patients, 59.5%), followed by megestrol acetate (MA) at 160–320 mg daily (38 patients, 31.4%), and dydrogesterone at 20–40 mg daily (11 patients, 9.1%). Among MPA-treated patients, 62 (86.1%) received doses of 400 mg/day or higher,

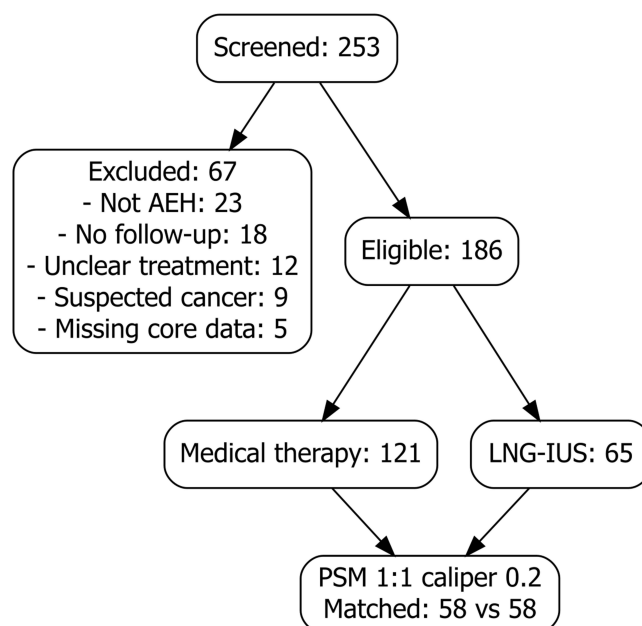


Figure 1 Patient Selection and Propensity Score Matching Flowchart.

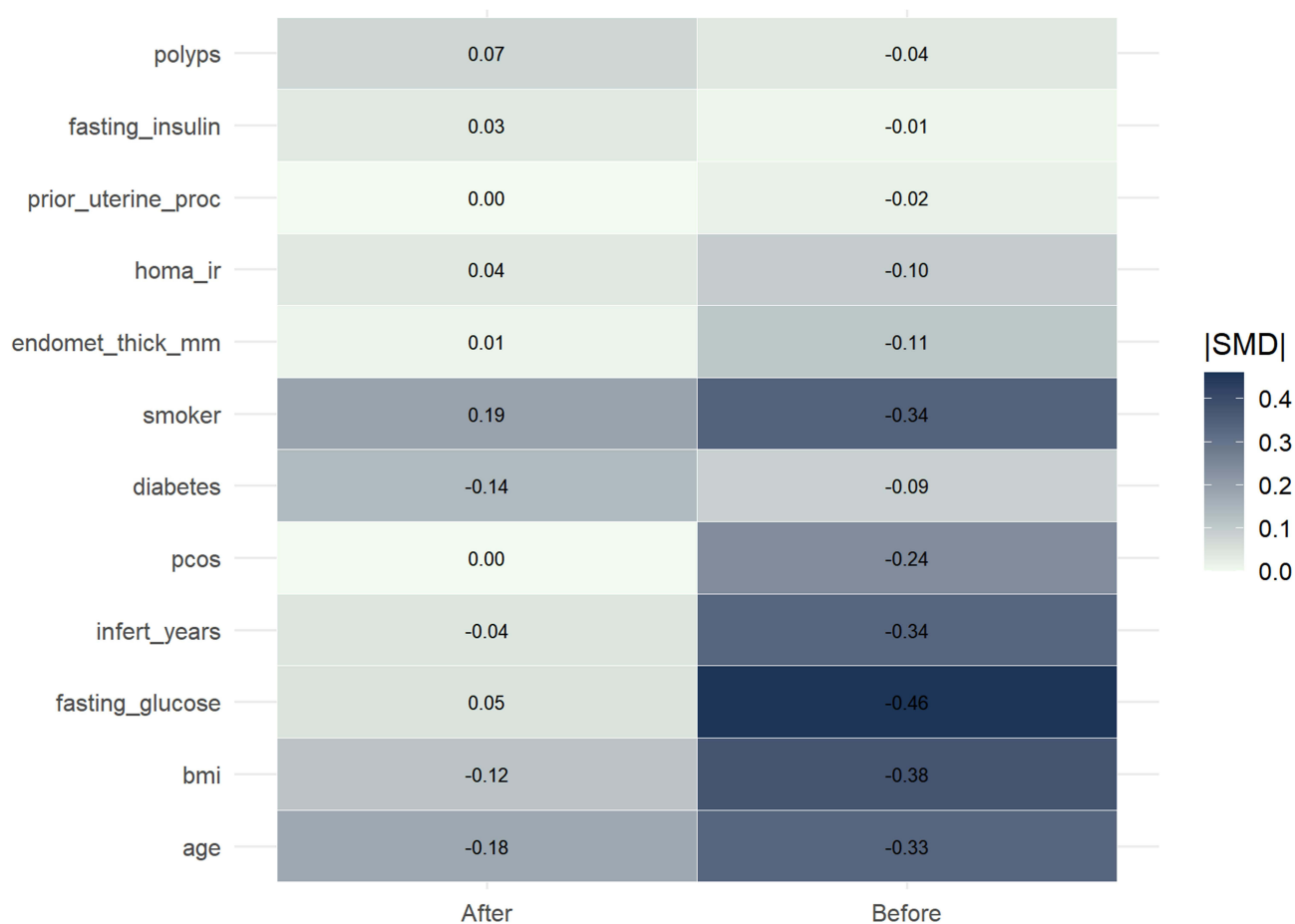


Figure 2 Covariate Balance Heatmap (Pre- and Post-Matching).

Table 1 Baseline Characteristics and Propensity Score Balance (Unmatched and PSM Cohorts)

Variable	Unmatched: Medical Therapy (n=121)	Unmatched: LNG-IUS (n=65)	SMD	P-value	PSM: Medical Therapy (n=58)	PSM: LNG-IUS (n=58)	SMD	P-value
Age (years), mean±SD	32.4±4.8	30.8±4.2	0.35	0.021	31.2±4.5	31.0±4.3	0.04	0.78
BMI (kg/m ²), mean±SD	27.8±5.2	25.9±4.6	0.38	0.012	26.5±4.8	26.2±4.7	0.06	0.72
Infertility duration (years), median [IQR]	2.5 [1.5–4.0]	2.0 [1.0–3.5]	0.28	0.067	2.3 [1.5–3.8]	2.2 [1.2–3.5]	0.08	0.64
PCOS, n (%)	58 (47.9)	26 (40.0)	0.16	0.29	24 (41.4)	23 (39.7)	0.04	0.84
Concurrent polyps, n (%)	34 (28.1)	22 (33.8)	0.12	0.39	18 (31.0)	19 (32.8)	0.04	0.84
Baseline endometrial thickness (mm), mean±SD	13.2±3.8	12.5±3.4	0.19	0.19	12.8±3.6	12.6±3.5	0.06	0.75
Fasting glucose (mg/dL), mean±SD	98.4±14.6	95.2±12.8	0.23	0.13	96.8±13.7	95.9±13.2	0.07	0.71
Fasting insulin (μU/mL), median [IQR]	14.8 [10.2–22.5]	12.6 [8.9–19.2]	0.31	0.048	13.5 [9.8–20.1]	13.2 [9.2–19.8]	0.07	0.68
HOMA-IR, median [IQR]	3.6 [2.4–5.8]	3.0 [2.0–4.9]	0.28	0.072	3.2 [2.2–5.2]	3.1 [2.1–5.0]	0.06	0.76
Diabetes mellitus, n (%)	12 (9.9)	4 (6.2)	0.14	0.37	5 (8.6)	4 (6.9)	0.06	0.73
Current smoker, n (%)	8 (6.6)	3 (4.6)	0.09	0.57	3 (5.2)	3 (5.2)	0.00	1.00
Prior uterine procedures, n (%)	28 (23.1)	17 (26.2)	0.07	0.63	15 (25.9)	16 (27.6)	0.04	0.83

Abbreviations: AEH, atypical endometrial hyperplasia; BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; IQR, interquartile range; LNG-IUS, levonorgestrel-releasing intrauterine system; PCOS, polycystic ovary syndrome; PSM, propensity score matching; SD, standard deviation; SMD, standardized mean difference.

Table 2 Initial Treatment Regimens and Disease Response

Parameter	Medical Therapy Group	LNG-IUS Group	Test Statistic	P-value
Initial Treatment Regimen				
MPA 400–600 mg/day, n (%)	72 (59.5)	—	—	—
MA 160–320 mg/day, n (%)	38 (31.4)	—	—	—
Dydrogesterone 20–40 mg/day, n (%)	11 (9.1)	—	—	—
Adjuvant metformin, n (%)	43 (35.5)	18 (27.7)	$\chi^2=1.24$	0.27
Treatment Duration and Response				
Treatment duration to CR (months), median [IQR]	6.0 [4.5–9.0]	6.0 [4.0–9.0]	U=3685	0.82
Complete remission achieved, n (%)	96 (79.3)	55 (84.6)	$\chi^2=0.83$	0.36
Time to CR (months), median [IQR]	6.0 [4.0–8.5]	5.5 [4.0–8.0]	HR 1.18 (0.85–1.63)	0.33
Partial response, n (%)	14 (11.6)	6 (9.2)	$\chi^2=0.27$	0.60
No response, n (%)	11 (9.1)	4 (6.2)	$\chi^2=0.57$	0.45
Treatment crossover, n (%)	18 (14.9)	7 (10.8)	$\chi^2=0.70$	0.40

Note: “—” indicates not applicable.

Abbreviations: CI, confidence interval; CR, complete remission; HR, hazard ratio; IQR, interquartile range; LNG-IUS, levonorgestrel-releasing intrauterine system; MA, megestrol acetate; MPA, medroxyprogesterone acetate.

while 10 patients (13.9%) received 250 mg/day, reflecting dose adjustments for tolerability or metabolic concerns. Adjuvant metformin therapy (1500–2000 mg daily) was prescribed to 43 patients (35.5%) with PCOS or insulin resistance. The LNG-IUS group received the 52 mg levonorgestrel intrauterine system (Mirena®), typically maintained for the entire treatment and follow-up period.

Primary Pregnancy Outcomes

Primary pregnancy outcomes for the propensity score-matched cohort are presented in Table 3, representing the main findings of this study. Complete remission was achieved in 45 of 58 patients (77.6%) in the medical therapy group and 49 of 58 patients (84.5%) in the LNG-IUS group (adjusted OR 1.52, 95% CI 0.71–3.26, $p=0.28$). Among patients achieving CR who attempted conception, clinical pregnancy was documented in 23 of 45 patients (51.1%) in the medical therapy group compared to 33 of 49 patients (67.3%) in the LNG-IUS group. Median time to pregnancy was 8.5 months (IQR 6–14) versus 6.0 months (IQR 4–10) (HR 1.64, 95% CI 1.12–2.41, $p=0.011$) (Figure 4). Live birth rates were 37.8% (17/45) in the medical therapy group versus 55.1% (27/49) in the LNG-IUS group (adjusted OR 2.28, 95% CI 1.13–4.62, $p=0.022$).

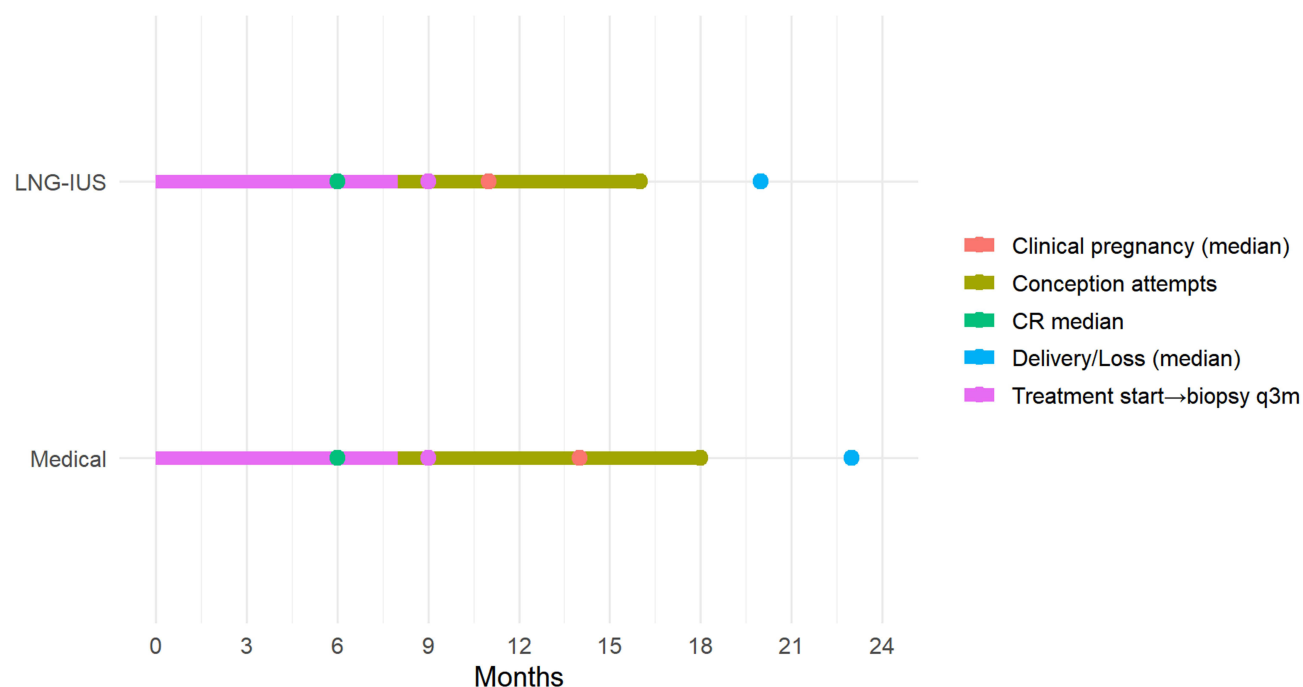


Figure 3 Treatment Timeline from Initiation to Pregnancy Outcomes.

Per-Protocol Analysis

In the per-protocol analysis excluding crossover patients (15 from the medical therapy group and 5 from the LNG-IUS group within the PSM cohort), results were consistent with the intention-to-treat findings. Among per-protocol patients achieving CR, clinical pregnancy rates were 48.7% (19/39) in the medical therapy group versus 68.2% (30/44) in the LNG-IUS group (adjusted OR 2.31, 95% CI 1.04–5.12, $p=0.039$). Live birth rates were 35.9% (14/39) versus 56.8% (25/44) (adjusted OR 2.42, 95% CI 1.05–5.57, $p=0.038$). Median time to pregnancy was 9.0 months (IQR 6–15) versus 5.5 months (IQR 4–9) (HR 1.72, 95% CI 1.08–2.74, $p=0.023$). These per-protocol results confirm the robustness of the ITT findings and indicate that treatment crossover did not substantially confound the observed treatment effects. Additionally, sensitivity analysis restricted to patients receiving MPA ≥ 400 mg/day in the medical therapy group yielded similar results (clinical pregnancy rate 53.8%, live birth rate 40.4%), suggesting that the dosage heterogeneity in the medical therapy group did not disproportionately drive the observed difference.

Secondary Outcomes and ART Utilization

Secondary reproductive outcomes are summarized in Table 4. Assisted reproductive technology was utilized by 55.6% (25/45) of medical therapy patients and 61.2% (30/49) of LNG-IUS patients ($p=0.57$). Among patients using ART, the most common procedures were controlled ovarian hyperstimulation with timed intercourse (18 patients, 32.7%),

Table 3 Primary Pregnancy Outcomes (Propensity Score-Matched Cohort)

Outcome	Medical Therapy n/N (%)	LNG-IUS n/N (%)	Absolute Difference (%)	Adjusted Effect Estimate (95% CI)	P-value
Complete remission	45/58 (77.6)	49/58 (84.5)	+6.9	OR: 1.52 (0.71–3.26)	0.28
Clinical pregnancy	23/45 (51.1)	33/49 (67.3)	+16.2	OR: 2.14 (1.08–4.25)	0.029
Live birth	17/45 (37.8)	27/49 (55.1)	+17.3	OR: 2.28 (1.13–4.62)	0.022
Time to pregnancy (months), median [IQR]	8.5 [6.0–14.0]	6.0 [4.0–10.0]	–2.5	HR: 1.64 (1.12–2.41)	0.011

Note: Bold text indicates co-primary endpoints.

Abbreviations: CI, confidence interval; HR, hazard ratio; IQR, interquartile range; LNG-IUS, levonorgestrel-releasing intrauterine system; OR, odds ratio.

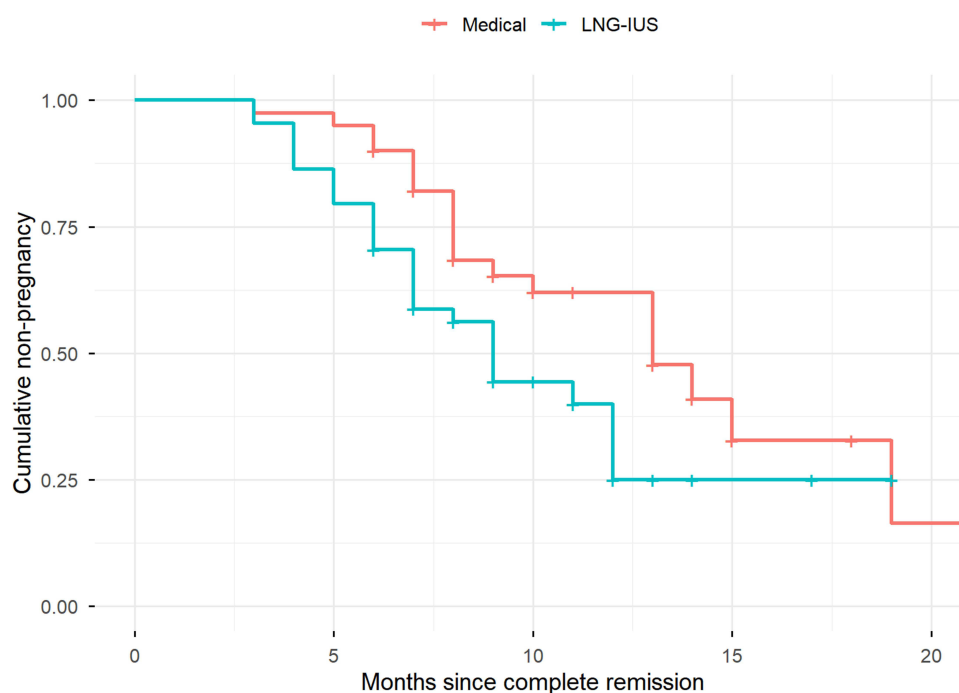


Figure 4 Time to Pregnancy by Treatment Group.

intrauterine insemination (15 patients, 27.3%), conventional IVF (14 patients, 25.5%), and ICSI (8 patients, 14.5%). Spontaneous conception without medical intervention occurred in 44.4% (20/45) of the medical therapy group versus 38.8% (19/49) of the LNG-IUS group (adjusted OR 0.79, 95% CI 0.38–1.65, $p=0.53$).

Predictive Factors for Live Birth

Multivariable logistic regression analysis identified several significant predictors of live birth following fertility-sparing treatment (Table 5) (Figure 5). After adjusting for treatment modality and other covariates, younger age at diagnosis (per 5-year decrease: adjusted OR 1.68, 95% CI 1.14–2.48, $p=0.009$), lower BMI (per 5 kg/m² decrease: adjusted OR 1.52, 95% CI 1.08–2.14, $p=0.017$), shorter time to complete remission (per 3-month decrease: adjusted OR 1.34, 95% CI 1.02–1.77, $p=0.035$), and ART utilization (vs. spontaneous conception: adjusted OR 2.86, 95% CI 1.35–6.05, $p=0.006$) were independently associated with higher odds of live birth. Treatment with LNG-IUS versus medical therapy showed a strong positive association (adjusted OR 2.28, 95% CI 1.13–4.62, $p=0.022$).

Table 4 Secondary Outcomes

Outcome	Medical Therapy	LNG-IUS	Adjusted Effect (95% CI)	P-value
Spontaneous conception rate, n (%)	20/45 (44.4)	19/49 (38.8)	OR: 0.79 (0.38–1.65)	0.53
ART utilization rate, n (%)	25/45 (55.6)	30/49 (61.2)	OR: 1.27 (0.62–2.58)	0.52
First-trimester miscarriage, n (%)	5/23 (21.7)	5/33 (15.2)	OR: 0.64 (0.17–2.39)	0.51
Second-trimester loss, n (%)	1/23 (4.3)	1/33 (3.0)	OR: 0.69 (0.04–11.42)	0.79
Pre-conception AEH recurrence, n (%)	8/45 (17.8)	4/49 (8.2)	SHR: 0.42 (0.13–1.38)	0.15
Time to recurrence (months), median [IQR]	14.5 [10.0–22.0]	16.0 [12.0–24.0]	—	0.62
Postpartum AEH recurrence, n (%)	3/17 (17.6)	2/27 (7.4)	SHR: 0.38 (0.06–2.31)	0.29

Note: Bold text indicates disease recurrence endpoints.

Abbreviations: AEH, atypical endometrial hyperplasia; ART, assisted reproductive technology; CI, confidence interval; IQR, interquartile range; LNG-IUS, levonorgestrel-releasing intrauterine system; OR, odds ratio; SHR, subdistribution hazard ratio from Fine-Gray competing risks model.

Table 5 Multivariable Analysis of Factors Associated with Live Birth

Variable	Adjusted OR (95% CI)	P-value	Notes
Treatment (LNG-IUS vs. Medical Therapy)	2.28 (1.13–4.62)	0.022	Reference: Medical therapy
Age (per 5-year increase)	0.60 (0.40–0.88)	0.009	Continuous variable; OR <1.0 indicates younger age favors live birth
BMI (per 5 kg/m ² increase)	0.66 (0.47–0.93)	0.017	Continuous variable; OR <1.0 indicates lower BMI favors live birth
PCOS (yes vs. no)	0.78 (0.38–1.60)	0.50	Binary variable
Insulin resistance (yes vs. no)	0.72 (0.34–1.52)	0.39	HOMA-IR ≥2.5
Time to CR (per 3-month increase)	0.75 (0.57–0.98)	0.035	Continuous variable; OR <1.0 indicates shorter time favors live birth
ART utilization (yes vs. no)	2.86 (1.35–6.05)	0.006	Binary variable
Concurrent polyps (yes vs. no)	0.89 (0.40–1.98)	0.77	Binary variable
Metformin use (yes vs. no)	1.42 (0.66–3.05)	0.37	Adjuvant therapy

Abbreviations: ART, assisted reproductive technology; BMI, body mass index; CI, confidence interval; CR, complete remission; HOMA-IR, homeostatic model assessment of insulin resistance; LNG-IUS, levonorgestrel-releasing intrauterine system; OR, odds ratio; PCOS, polycystic ovary syndrome.

Treatment-Related Adverse Events

Treatment-related adverse events are summarized in Table 6. In the medical therapy group, the most frequent adverse effects included weight gain ≥5 kg (42 patients, 34.7%), menstrual irregularities (38 patients, 31.4%), mood disturbances (29 patients, 24.0%), and gastrointestinal symptoms (21 patients, 17.4%). Liver function abnormalities (ALT/AST elevation >2× upper limit of normal) were observed in 5 patients (4.1%) in the medical therapy group and none in the LNG-IUS group; all cases were transient Grade 1–2 elevations that normalized after dose reduction or discontinuation, and no cases of clinically significant hepatotoxicity occurred. Liver function was monitored at baseline and every 3 months during treatment. Grade 3 or higher adverse events were uncommon but included thromboembolic events (2 patients, 1.7%), requiring treatment discontinuation and anticoagulation therapy. Regarding the two thromboembolic events in the medical therapy group, both patients developed lower-extremity deep vein thrombosis (DVT) confirmed by

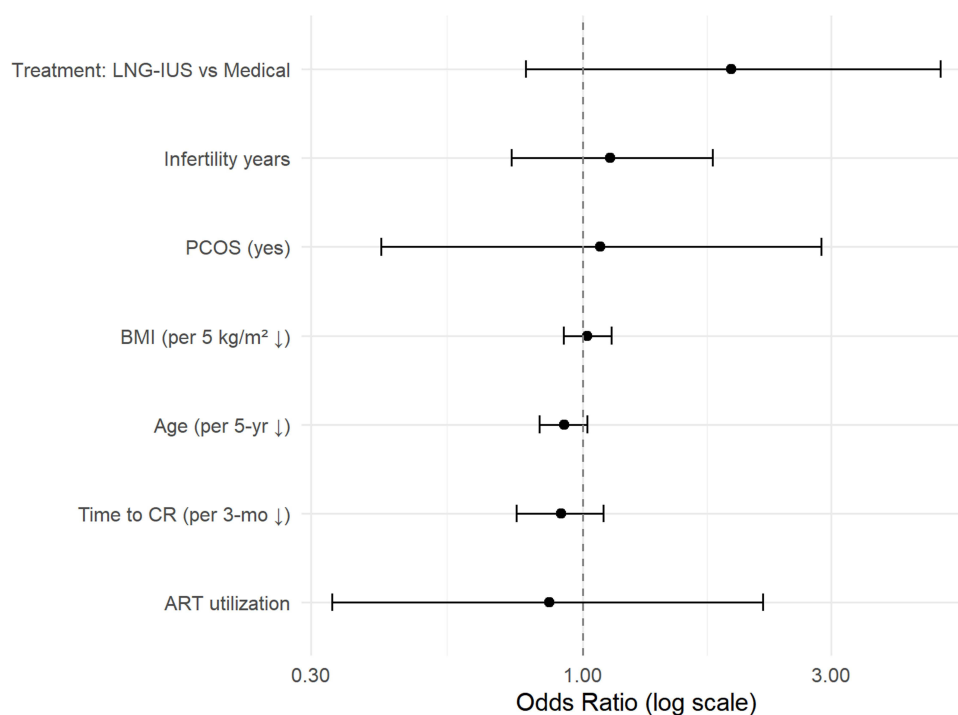


Figure 5 Predictors of Live Birth in Matched Cohort. Dots represent adjusted odds ratios, with horizontal lines indicating 95% confidence intervals. The vertical dashed line at OR=1.0 denotes no effect. For continuous variables, downward arrows (↓) in the variable labels indicate that the odds ratio corresponds to a decrease in that variable (eg, “per 5-yr ↓” means per 5-year decrease in age). An OR >1.0 indicates higher odds of live birth.

Table 6 Treatment-Related Adverse Events

Adverse Event	Medical Therapy n (%)	LNG-IUS n (%)	Grade (CTCAE)	Management	Outcome
Weight gain (≥ 5 kg)	42 (34.7)	8 (12.3)	Grade 1–2	Lifestyle counseling, dietary consultation	Continued treatment; 12 patients lost weight with intervention
Mood changes	29 (24.0)	6 (9.2)	Grade 1–2	Supportive care (n=30), psychiatric referral (n=5)	Continued treatment; 3 required dose reduction
Gastrointestinal symptoms	21 (17.4)	3 (4.6)	Grade 1–2	Symptomatic treatment, metoclopramide PRN	Resolved in 18, tolerable in 6
Liver enzyme elevation ($>2\times$ ULN)	5 (4.1)	0 (0)	Grade 1–2	Dose reduction or discontinuation	Normalized in all patients; no severe hepatotoxicity
Thromboembolic event (DVT)	2 (1.7)	0 (0)	Grade 3	Treatment discontinuation, anticoagulation therapy	Resolved; switched to LNG-IUS after 3 months
Device expulsion	—	5 (7.7)	Grade 2	Replacement attempted (successful n=3); alternative treatment (n=2)	3 continued LNG-IUS, 2 switched to MPA
Device malposition	—	3 (4.6)	Grade 2	Removal and repositioning under ultrasound	All successfully repositioned
Persistent bleeding/spotting	18 (14.9)	4 (6.2)	Grade 1	Observation (n=16), tranexamic acid (n=6)	Resolved in 20, persistent but tolerable in 2
Pelvic inflammatory disease	0 (0)	1 (1.5)	Grade 3	Device removal, ceftriaxone + doxycycline 14 days	Complete resolution; successful MPA treatment subsequently
Treatment discontinuation due to AE	8 (6.6)	7 (10.8)	Varies	Switch to alternative therapy	All eventually achieved satisfactory treatment

Note: “—” indicates not applicable.

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events v5.0; DVT, deep vein thrombosis; LNG-IUS, levonorgestrel-releasing intrauterine system; MPA, medroxyprogesterone acetate; PRN, as needed; ULN, upper limit of normal.

compression ultrasonography with Doppler, at 4.5 and 7 months after treatment initiation, respectively. Risk factor assessment revealed that one patient had BMI of 34.2 kg/m^2 and the other had concurrent PCOS with HOMA-IR of 5.8, representing pre-existing risk factors compounded by high-dose progestin use. Both patients received anticoagulation with low-molecular-weight heparin followed by oral rivaroxaban for 3 months, after which progestin therapy was discontinued and they were transitioned to LNG-IUS treatment following resolution. No pulmonary embolism or major hemorrhagic complications occurred. While a DVT rate of 1.7% appears relatively high, it is consistent with rates reported in populations receiving high-dose progestins combined with obesity and metabolic risk factors.²⁴ In the LNG-IUS group, device-related complications occurred in 18.5% (12/65) of patients, including expulsion (5 patients, 7.7%), malposition requiring removal (3 patients, 4.6%), and persistent spotting lasting >6 months (4 patients, 6.2%). One patient (1.5%) developed pelvic inflammatory disease requiring device removal and antibiotic therapy, which resolved completely.

Discussion

This retrospective cohort study compared pregnancy outcomes between systemic progestin therapy and LNG-IUS treatment in women with AEH desiring fertility preservation. Our findings demonstrate that LNG-IUS treatment was associated with significantly higher clinical pregnancy rates (67.3% vs. 51.1%, adjusted OR 2.14, $p=0.029$), higher live birth rates (55.1% vs. 37.8%, adjusted OR 2.28, $p=0.022$), and shorter time to pregnancy (median 6.0 vs. 8.5 months, HR 1.64, $p=0.011$) compared to systemic progestin therapy. These results provide clinicians with real-world evidence supporting LNG-IUS as a preferred fertility-sparing option for reproductive-age women with AEH, particularly when expedited conception is clinically desirable.

The complete remission rates observed in both treatment groups (77.6% for medical therapy, 84.5% for LNG-IUS) are consistent with published systematic reviews and meta-analyses reporting CR rates of 75–82% for oral progestins and 79–87% for LNG-IUS.^{25,26} Our institutional experience demonstrates similar oncologic efficacy, supporting the viability of both therapeutic modalities for achieving disease control. The mechanism underlying progestin efficacy involves progesterone receptor-mediated suppression of estrogen-driven endometrial proliferation, induction of secretory transformation, and promotion of apoptosis in hyperplastic cells.²⁷ LNG-IUS delivers sustained high local progestin concentrations;

pharmacokinetic studies by Nilsson et al demonstrated that endometrial tissue levonorgestrel concentrations with LNG-IUS are approximately 100–1000 times higher than those achieved with systemic administration, depending on the distance from the device and the tissue compartment sampled.²⁸ These markedly elevated local concentrations may enhance antiproliferative effects while minimizing systemic exposure and associated metabolic disturbances.²⁹

The superior pregnancy outcomes observed with LNG-IUS treatment warrant mechanistic consideration. Several biologic pathways may explain these differences in reproductive success. First, LNG-IUS provides continuous local progestin delivery at therapeutic concentrations throughout the treatment period, potentially producing more complete endometrial suppression and reducing subclinical disease persistence that might impair subsequent implantation competence.³⁰ The localized drug delivery achieves potent endometrial effects sufficient for disease regression while preserving hypothalamic-pituitary-ovarian axis function more effectively than high-dose systemic progestins. This preservation of normal ovulatory function may facilitate natural conception and improve endometrial receptivity during implantation windows.³¹

Second, the substantially lower systemic hormone exposure with LNG-IUS results in reduced metabolic perturbations compared to oral progestins. High-dose systemic progestins commonly induce weight gain averaging 3–5 kg during treatment courses, exacerbate insulin resistance particularly in PCOS patients, and can worsen existing metabolic dysfunction.³² In our cohort, weight gain ≥ 5 kg occurred in 34.7% of medical therapy patients versus only 12.3% of LNG-IUS patients. Given the high baseline prevalence of obesity (mean BMI 26–28 kg/m²) and PCOS (40–48%) in AEH populations, minimizing additional metabolic burden may be particularly important for optimizing fertility potential. Our multivariable analysis confirmed that lower BMI was independently associated with higher live birth rates (adjusted OR 1.52 per 5 kg/m² decrease, $p=0.017$), suggesting that treatment-related weight gain with systemic progestins could compound preexisting fertility barriers.

Third, the improved tolerability profile of LNG-IUS may enhance treatment adherence and reduce interruptions that compromise oncologic control. We observed treatment discontinuation rates of 6.6% for medical therapy versus 10.8% for LNG-IUS, primarily reflecting device-related mechanical issues (expulsion, malposition) rather than intolerable systemic symptoms. However, among patients continuing treatment, LNG-IUS patients experienced fewer troublesome adverse effects requiring management modifications. This improved tolerability may translate to more consistent disease suppression, more reliable achievement of complete remission, and ultimately better preserved endometrial function for subsequent implantation.

The role of assisted reproductive technology in this population merits particular emphasis given our findings. ART utilization emerged as the strongest independent predictor of live birth success (adjusted OR 2.86, 95% CI 1.35–6.05, $p=0.006$), consistent with prior literature demonstrating 39–45% live birth rates with IVF versus 15–20% with expectant management.^{21,33} This observation reflects multiple contributing factors. Many AEH patients present with baseline infertility due to chronic anovulation (particularly those with PCOS), tubal factors, diminished ovarian reserve, or advanced maternal age, making spontaneous conception biologically improbable regardless of successful AEH treatment.³⁴ The median age in our cohort (31 years) and substantial PCOS prevalence (40–48%) support this interpretation. Additionally, the clinical urgency of achieving pregnancy before potential disease recurrence creates a compelling rationale for aggressive fertility interventions rather than prolonged expectant management trials.³⁵

Our data suggest that while LNG-IUS treatment improved overall pregnancy rates, the benefit was evident in both spontaneous and ART-assisted conception subgroups. This finding implies that the mechanisms underlying LNG-IUS superiority extend beyond simple preservation of ovulatory function to include optimization of endometrial quality and receptivity that benefit all conception pathways. Clinicians counseling patients should emphasize that fertility preservation treatment selection and conception method determination represent independent but complementary decisions. Even patients planning ART may benefit from LNG-IUS treatment given the superior endometrial preparation and potentially lower disease recurrence risk during the peri-conception period.

The recurrence patterns observed in our propensity-matched cohort deserve careful consideration. Pre-conception recurrence occurred in 17.8% of medical therapy patients versus 8.2% of LNG-IUS patients (SHR 0.42, 95% CI 0.13–1.38, $p=0.15$), demonstrating a numerical trend toward lower recurrence with LNG-IUS that did not achieve statistical significance in our sample size. These rates are somewhat lower than historical reports citing 26–33% recurrence for oral progestins and 11–14% for LNG-IUS,^{10,17} likely reflecting our propensity matching process selecting lower-risk patients with better prognostic features. The biological mechanisms underlying differential recurrence risk

likely involve more complete suppression of molecular alterations driving hyperplastic transformation, more sustained progesterone receptor engagement in morphologically normal-appearing endometrium, and potentially epigenetic modifications favoring differentiated phenotypes over proliferative states.^{36,37}

The postpartum recurrence rates observed (17.6% after medical therapy, 7.4% after LNG-IUS) underscore the importance of continued surveillance following successful pregnancy outcomes. The protective effect of pregnancy against recurrence, mediated through prolonged endogenous progesterone exposure, decidualization, and lactational amenorrhea, appears substantial but not absolute.³⁸ These findings support current guideline recommendations for endometrial sampling within 3–6 months postpartum and consideration of definitive hysterectomy once childbearing is complete, particularly in patients with high-risk features such as persistent obesity, insulin resistance, or prior recurrence episodes.

Our multivariable analysis identified clinically relevant predictive factors beyond treatment modality selection. Younger age at diagnosis (adjusted OR 1.68 per 5-year decrease) represents a consistent predictor of favorable outcomes across fertility preservation literature, reflecting both superior baseline reproductive capacity and shorter cumulative duration of unopposed estrogen exposure.³⁹ This finding supports aggressive fertility-sparing approaches in women under 35 years, while warranting enhanced counseling regarding success likelihood and expedited ART consideration for women approaching 35–40 years. Body mass index demonstrated a strong inverse relationship with pregnancy success (adjusted OR 1.52 per 5 kg/m² decrease), consistent with extensive literature documenting obesity's negative impact through insulin resistance, chronic anovulation, altered estrogen metabolism, and relative ART treatment resistance.⁴⁰

Shorter time to complete remission independently predicted better reproductive outcomes (adjusted OR 1.34 per 3-month decrease, $p=0.035$), likely reflecting favorable tumor biology and preserved endometrial function.⁴¹ Metformin showed a non-significant trend toward improved live birth rates (adjusted OR 1.42, 95% CI 0.66–3.05, $p=0.37$), contrasting with randomized trials demonstrating higher complete response rates (OR 2.08–1.86) with combination progestin-plus-metformin therapy.^{42–44} The mechanistic rationale includes progesterone receptor upregulation, down-regulation of mTOR and insulin-like growth factor pathways, improved insulin sensitivity, and direct antiproliferative effects through AMPK activation.⁴⁵ Current evidence supports liberal metformin use in patients with BMI ≥ 25 kg/m², insulin resistance (HOMA-IR ≥ 2.5), or PCOS given its favorable safety profile and potential dual benefits.⁴⁶ Safety profile comparison revealed expected differences: systemic progestins caused weight gain (34.7%), mood alterations (24.0%), liver function abnormalities (4.1%), and rare thromboembolic events (1.7%) requiring careful baseline risk assessment,⁴⁷ while LNG-IUS complications were predominantly device-specific including expulsion (7.7%), malposition (4.6%), and one case of pelvic inflammatory disease (1.5%). The lower systemic hormone exposure with LNG-IUS substantially reduces metabolic disturbances, particularly advantageous for obese patients or those with cardiovascular risk factors.⁴⁸ Patient counseling should incorporate these differential safety considerations alongside efficacy data to support individualized treatment selection aligned with patient values and preferences rather than universal protocols.

This single-center retrospective cohort study has several important limitations that must be considered when interpreting our findings. First, non-randomized treatment allocation introduces potential selection bias; notably, the unmatched LNG-IUS group was significantly younger and had lower BMI, suggesting that clinicians may have preferentially assigned lower-risk patients to LNG-IUS therapy. Although propensity score matching substantially reduced these imbalances, residual confounding by unmeasured variables (such as patient preference, physician recommendation patterns, or subclinical disease features) cannot be excluded. Second, the medical therapy group included heterogeneous progestin regimens with variable dosages (MPA 250–600 mg/day), with the lower end of dosing (250 mg/day) potentially below optimal oncologic thresholds. While sensitivity analysis restricted to patients receiving MPA ≥ 400 mg/day yielded similar results, this dosage variability may have biased outcomes against the medical therapy group to some extent. Third, limited generalizability from the tertiary care setting, modest sample size (116 matched patients) reducing statistical power for subgroup analyses, median follow-up of only 36 months that may be insufficient for capturing long-term recurrence patterns, and absence of molecular classification data that could inform risk stratification represent additional constraints. Despite these limitations, our findings provide valuable real-world evidence that LNG-IUS treatment was associated with superior outcomes compared to systemic progestin therapy, with higher pregnancy rates, higher live birth rates, and shorter time to conception. Both the ITT and per-protocol analyses yielded consistent conclusions, strengthening confidence in the observed treatment effects. Clinical implications include preferential use of LNG-IUS as first-line therapy for most AEH

patients, early fertility specialist involvement post-remission, comprehensive metabolic optimization given the strong inverse relationship between BMI and live birth success, and close endometrial surveillance during and after treatment.

In conclusion, this study provides evidence that LNG-IUS treatment is associated with superior pregnancy outcomes compared to systemic progestin therapy in women with atypical endometrial hyperplasia desiring fertility preservation. The combination of higher pregnancy rates, higher live birth rates, and shorter time to conception supports preferential consideration of LNG-IUS for most patients, while individualized treatment selection based on patient characteristics, preferences, and contraindications remains essential. These conclusions should be tempered by the inherent limitations of the retrospective design, including the heterogeneous dosing in the medical therapy group and the potential for residual selection bias. Future research should focus on prospective randomized controlled trials with standardized progestin dosing, molecular profiling for precision medicine approaches, optimization of ART timing and protocols, and long-term oncologic and reproductive outcome studies to provide women facing this diagnosis with the best possible chance of achieving both disease control and their childbearing goals.

Data Sharing Statement

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

Ethical Approval

The Ethics Committee of Wuxi Maternity and Child Health Care Hospital approved this retrospective investigation (Approval Number: IEC-FOM-17015). This study was conducted in compliance with the Declaration of Helsinki. All patients signed informed consent forms.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Min Wang and Shaojie Zhao are co-first authors for this study. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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