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REPRODUCTIVE OUTCOMES IN PATIENTS WITH ENDOMETRIAL HYPERPLASIA AFTER FERTILITY-SPARING TREATMENT – A CASE SERIES

Reproductive Medicine

Dr P Seeniammal* Fellow in Reproductive Medicine, Institute of Reproductive Medicine, MMM Hospital, Chennai *Corresponding Author
Dr KM Kundavi HOD, Institute of Reproductive Medicine, MMM Hospital, Chennai
Dr GV Rashmi Consultant, Institute of Reproductive Medicine, MMM Hospital, Chennai
Dr V Geetha Consultant, Institute of Reproductive Medicine, MMM Hospital, Chennai
Dr G Geovin Ranji Consultant, Institute of Reproductive Medicine, MMM Hospital, Chennai

ABSTRACT

Purpose: To evaluate the clinical efficacy of conservative progesterone therapy in achieving histological reversal in patients with endometrial hyperplasia (EH) and to assess their subsequent reproductive outcomes following assisted reproductive technology (ART) or spontaneous conception. **Methods:** This retrospective case series was conducted at the Department of Reproductive Medicine (IRM), Madras Medical Mission, Chennai, between January 2021 and January 2026. Seven patients with a documented diagnosis of EH (six with non-atypical EH and one with atypical EH) who desired future pregnancy and opted for fertility-sparing treatment (FST) were included. Primary outcomes included the rate of histological remission, time to reversal, and reproductive outcomes (clinical pregnancy and live birth rates). **Results:** The cohort consisted of seven patients with a median age of 36 years. Obesity (86%) and Polycystic Ovary Syndrome (PCOS, 43%) were the predominant risk factors. Diminished Ovarian Reserve (DOR) was identified in 29% of cases. Complete histological reversal was achieved in all patients (n=7) within a median of 3 months (range 3–8 months). Following remission, six patients with non-atypical EH pursued pregnancy. Four patients (67%) achieved clinical pregnancy, resulting in two miscarriages and two live births. The patient with atypical EH experienced recurrence and ultimately underwent total laparoscopic hysterectomy. The overall clinical pregnancy rate was 57%, and the live birth rate was 28.5%. **Conclusions:** Progesterone-based FST is an effective strategy for achieving remission in women with EH, allowing for the preservation of reproductive potential. While high remission rates are achievable, reproductive outcomes remain modest, particularly in patients with co-existing metabolic risk factors or DOR. Close multidisciplinary surveillance and optimized ART protocols are essential for maximizing success in this unique patient

KEYWORDS

Endometrial hyperplasia, fertility-sparing treatment, progesterone therapy, reproductive outcomes, PCOS, obesity, diminished ovarian reserve, case series

INTRODUCTION

Endometrial carcinoma is a significant gynaecologic malignancy, and its precursor, endometrial hyperplasia (EH), represents a critical clinical challenge in reproductive-aged women. According to the 2014 World Health Organization (WHO) classification, EH is categorized into non-atypical endometrial hyperplasia and atypical endometrial hyperplasia (also known as endometrial intraepithelial neoplasia, EIN) [1]. The risk of progression to malignancy is markedly higher in atypical cases (28–30%) compared to non-atypical cases (<5%) [1]

In recent years, there has been a global trend toward delayed childbearing, leading to an increased frequency of EH diagnoses in women who have not yet completed their families. For these patients, the standard treatment of total hysterectomy is often unacceptable. Fertility-sparing treatment (FST), primarily utilizing progestin therapy, has emerged as a safe and effective alternative for carefully selected patients. Progestins work by inducing stromal decidualization and endometrial thinning, thereby counteracting the proliferative effects of unopposed estrogen [1]

Common risk factors for EH include obesity and Polycystic Ovary Syndrome (PCOS), both of which are associated with chronic anovulation and hyperestrogenism [2,3]. Despite the high efficacy of FST in achieving histological remission, many patients require assisted reproductive technology (ART) to conceive. However, data on pregnancy outcomes following ART in this specific population remain limited. Furthermore, emerging evidence suggests that factors such as ovarian reserve may impact the duration of treatment required to achieve remission [4].

This study sought to evaluate the clinical efficacy of conservative progesterone therapy and the subsequent reproductive outcomes in a cohort of women treated at a tertiary fertility center, aiming to provide data that can aid in the counselling and management of this unique patient population.

MATERIALS AND METHODS

Design :

We conducted a retrospective case series study of all patients who underwent FST for EH at the Department of Reproductive Medicine (IRM), Madras Medical Mission, Chennai between January 2021 and February 2026. The study was conducted in accordance with the institutional guidelines and relevant regulations.

SUBJECTS:

Patients were identified through a review of electronic medical records. Inclusion criteria were: 1) a documented histological diagnosis of EH (atypical or non-atypical), 2) desire for future pregnancy, 3) willingness to undergo conservative progesterone treatment and regular follow-up, and 4) achievement of complete remission followed by attempts at conception (spontaneous or ART). A total of seven patients met the inclusion criteria.

VARIABLES AND STATISTICAL ANALYSIS

Data collected included age at diagnosis, parity, body mass index (BMI), risk factors (PCOS, obesity, DOR), type of fertility sparing treatment, time to histological reversal, number of frozen embryo transfer (FET) cycles, and pregnancy outcomes. The primary outcomes were the rate of histological reversal and the live birth rate (defined as the number of live births per patient). Secondary outcomes included clinical pregnancy rate and miscarriage rate. Descriptive data are presented as medians and ranges.

Treatment Protocol

Informed written consent was obtained from all patients. They were counselled on the necessity of repeat endometrial biopsies every 3–6 months, the risk of recurrence or progression, and the potential need for hysterectomy. Treatment regimens included:

- **Oral Progestins:** Norethisterone (10 mg OD) or Megestrol acetate (80 mg BD).
- **Intrauterine System:** Levonorgestrel-releasing intrauterine system (Mirena).
- **Adjunct Therapy:** Metformin was administered to all patients with obesity as an adjunct to progesterone as it inhibits the cancer cell proliferation

Embryo Transfer Protocol

Following confirmed histological reversal, patients proceeded to fertility treatment. All FET cycles were letrozole-stimulated. Endometrial thickness was monitored via ultrasound, with a mean thickness of 9.1 mm at the time of transfer. Clinical pregnancy was confirmed by the presence of a gestational sac on ultrasound.

RESULTS

A total of 14 patients were initially screened, and 7 patients met the criteria for inclusion: 6 (85.7%) with non-atypical EH and one (14.3%) with atypical EH.

The baseline demographics & individual characteristics are summarized in Table 1 & Table 2.

Table 1: Baseline Demographics of Patients with EH after FST

Variable	Total Cohort (n=7)	Non-atypical EH (n=6)	Atypical EH (n=1)
Median Age at Diagnosis (years)	36 (29–42)	36.5 (29–42)	33
Median BMI (kg/m²)	28.5 (24–34)	28.2 (24–34)	31
Obesity (BMI ≥ 30)	6 (86%)	5 (83%)	1 (100%)
PCOS	3 (43%)	2 (33%)	1 (100%)
Diminished Ovarian Reserve	2 (29%)	2 (33%)	0

Treatment and Remission

Complete histological reversal was achieved in all 7 patients (100%). The median time to reversal was 3 months (range 3–8 months). Patients with DOR (n=2) took a longer time to achieve remission (median 6.5 months) compared to those with normal reserve. Hysteroscopy performed prior to treatment revealed polypoidal endometrium in 67% of cases.

Table 2: Individual Characteristics and Outcomes

Diagnosis	Age in years	Risk factors	FST regimen	Time to reversal in months	FET cycles	Outcome
1.Non atypical EH	42	Obesity	NE*	5	2 (donor)	Live birth at 34W+5D (Twins)
2.Non atypical EH	39	Obesity	NE	8	2 (donor)	Live birth at 37W+5D (singleton)
3.Non atypical EH	37	Obesity, PCOS	NE	3	3	Negative
4.Non atypical EH	32	Obesity, PCOS	NE	3	2	Miscarriage (15 weeks)
5.Non atypical EH	29	None	Mirena	3	SC#	Miscarriage (8weeks)
6.Non atypical EH	36	Obesity	Mirena	3	1	Negative
7.Atypical EH	33	Obesity, PCOS	Megestrol	3	2	TLH^ for recurrence

* -NE –Norethisterone,#-SC-spontaneous conception,^-TLH-Total Laparoscoipc Hysterectomy

Reproductive Outcomes

Among the six patients with non-atypical EH who attempted conception:

- **Clinical Pregnancy Rate:** 66.7% (4/6).
- **Live Birth Rate:** 33.3%(2/6)
- **Miscarriage Rate:** 33.3% (2/6).

The patient with atypical EH, underwent two FET cycles without achieving conception. During follow-up, she experienced a recurrence of atypical EH during her followup within 11months of remission and opted for Total Laparoscopic Hysterectomy (TLH) with bilateral salpingo-oophorectomy (BSO).

DISCUSSION

This study demonstrates that conservative progesterone therapy is highly effective in achieving histological remission in women with EH, with a 100% reversal rate in our cohort. This finding is consistent with the established efficacy of progestins in treating EH . However, the transition from histological remission to a successful live birth remains a significant hurdle, as evidenced by our clinical pregnancy rate of 57% and live birth rate of 14%.

Our results align with the findings of Friedlander et al. (2023), who reported a clinical pregnancy rate of 60% following embryo transfer in a similar population [6]. The relatively high miscarriage rate (33%) observed in our study is a point of concern and likely reflects the underlying metabolic disturbances common in this population. Obesity and PCOS, present in 86% and 43% of our patients respectively, are known to impair endometrial receptivity and increase the risk of early pregnancy loss [3]. The use of Metformin as an adjunct in our obese patients aimed to mitigate these risks, a strategy supported by the findings of Yang et al. (2020) [7].

A significant observation in our cohort was the impact of Diminished Ovarian Reserve (DOR) on the duration of treatment required for remission. Patients with DOR required a longer time to achieve reversal (up to 8 months). This observation is supported by Wu et al. (2024), who noted that DOR patients often have a more protracted course to remission [4]. This suggests that the local endometrial environment or receptor expression may be altered in women with low ovarian reserve, necessitating more prolonged or intensive hormonal therapy.

The case of atypical EH in our series underscores the persistent risk of recurrence and progression. Despite achieving initial remission, the patient experienced recurrence and ultimately required definitive surgery. This highlights the need for stringent surveillance and thorough patient counselling regarding the limitations of FST in atypical cases [6].

LIMITATIONS

The primary limitation of this study is the small sample size, which limits the generalizability of the findings. Additionally, the retrospective nature of the study may introduce inherent biases. However, as a case series from a specialized center, it provides valuable real-world data on the reproductive journey of these patients.

CONCLUSION

Progesterone-based fertility-sparing therapy is a viable and effective strategy for women with endometrial hyperplasia who desire to preserve their fertility. While high rates of histological remission can be achieved, the path to a live birth is complex and influenced by metabolic factors and ovarian reserve. A multidisciplinary approach involving gynecologic oncologists and fertility specialists is crucial for optimizing both oncologic safety and reproductive success. Future research should focus on identifying biomarkers of endometrial receptivity to better tailor post-remission fertility treatments.

Declaration

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