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Endometrial Atrophy as a Cause of Persistent Postpartum Abnormal Uterine Bleeding Following Long-term Progesterone Therapy: A Case Series of 40 Patients

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Abstract: Background: Objective: To evaluate a stepwise hormonal protocol for restoring endometrial thickness in postpartum abnormal uterine bleeding following prolonged progestin therapy.**Study Design:** Prospective case series.**Place and Duration of Study:** Department of Obstetrics and Gynecology, Zahedan University of Medical Sciences, Zahedan, Iran, from March 2021 to February 2024.**Methodology:** Thirty-eight women with persistent vaginal spotting beyond 42 days postpartum and a history of ≥5 weeks of 17-hydroxyprogesterone caproate (Proluton®) were studied. All had endometrial thickness ≤5.6 mm and normal TSH, prolactin, and free β-hCG. Lactating women received conjugated estrogens (1.25 mg/day); non-lactating or unresponsive cases received a combined oral contraceptive (ethinylestradiol/desogestrel) for 2–4 months. Treatment continued until amenorrhoea for ≥3 months and endometrial thickness ≥6 mm was achieved.**Results**: Mean endometrial thickness increased from 3.03±1.08 mm to 6.83±0.86 mm ($p<0.001$), and 84.2% of patients reached the ≥6 mm target. All 38 patients achieved complete cessation of bleeding. Proluton duration was inversely correlated with baseline endometrial thickness ($\rho= 0.673$, $p<0.001$) and positively correlated with treatment duration ($\rho=0.627$, $p<0.001$).**Conclusion:** A structured estrogen-first hormonal protocol effectively restores endometrial thickness and resolves bleeding in postpartum endometrial atrophy following prolonged progestin therapy, without compromising lactation.

Keywords: Postpartum abnormal uterine bleeding, endometrial atrophy, 17-hydroxyprogesterone caproate, conjugated estrogens, desogestrel.

INTRODUCTION

The prevention of spontaneous preterm birth (PTB) remains one of the most pressing challenges in modern obstetrics, given that PTB accounts for approximately 35% of neonatal deaths worldwide and is the leading cause of infant mortality among children younger than five years [1,2]. Progestogen therapy has been a cornerstone of PTB prophylaxis for over two decades, with 17-alpha-hydroxyprogesterone caproate (17-OHPC, Proluton®) being the most extensively studied formulation. The landmark randomized controlled trial by Meis et al. demonstrated that weekly intramuscular injections of 17-OHPC significantly reduced the rate of recurrent preterm delivery in women with a prior history of spontaneous PTB [3]. This finding has since been supported by numerous systematic reviews and meta-analyses, establishing prolonged progestin administration as the standard of care for high-risk

pregnancies, including singleton gestations with a short cervix, multiple pregnancies, and cases requiring cervical cerclage [4,5]. In clinical practice, it is not uncommon for patients to receive 17-OHPC from as early as 16–20 weeks of gestation through 34–36 weeks, thus accumulating many weeks of sustained progestin exposure.

While the benefits of progestin therapy in prolonging gestation are well-documented, the endometrial consequences of prolonged, high-dose progestin exposure during pregnancy have received comparatively little attention in the literature. It is a well-established pharmacological principle that the continuous presence of progestin causes down-regulation of both estrogen and progesterone receptors in the endometrium [6,7]. This receptor down-regulation leads to progressive endometrial atrophy, characterized histologically by glandular regression, stromal decidualization, and thinning of the functional layer [8]. Casper reported that endometrial atrophy resulting from prolonged progestin exposure may compromise the stromal support of blood vessels, leading to vascular dilatation and extravasation of blood [7]. Furthermore, progestin-induced vascular fragility has been implicated in the pathogenesis of abnormal uterine bleeding (AUB) associated with long-acting progestin-only contraceptives, where bleeding is thought to arise from abnormally fragile, dilated endometrial vessels [9,10].

In the postpartum setting, the clinical picture is further complicated by the hypoestrogenic state of lactation. During exclusive breastfeeding, elevated prolactin levels suppress ovarian estrogen production, thereby removing the proliferative drive necessary for endometrial regeneration [11]. This dual insult — progestin-induced receptor down-regulation from the antenatal period combined with postpartum estrogen deficiency — may create a particularly refractory form of endometrial atrophy that manifests as persistent, irregular spotting or light bleeding beyond the normal six-week period of lochial discharge. Despite the plausibility of this mechanism, the entity of "postpartum endometrial atrophy following prolonged progestin therapy" has not been formally described in the obstetrics literature.

Clinically, women presenting with abnormal uterine bleeding persisting beyond six weeks postpartum are typically evaluated for the usual suspects: retained products of conception (RPOC), endometritis, uterine vascular anomalies such as arteriovenous malformations (AVMs), and gestational trophoblastic disease [12,13]. When initial work-up — including transvaginal ultrasound and laboratory assessment of thyroid function, prolactin, and beta-hCG — is negative, clinicians may feel pressured to proceed with invasive diagnostic procedures such as hysteroscopy or dilatation and curettage. In the context of an already thin and atrophic endometrium, such interventions may cause further iatrogenic damage to the basal layer, potentially leading to intrauterine adhesions and future reproductive compromise [14].

These considerations highlight an important gap in the literature: the absence of a defined pharmacological strategy for managing persistent postpartum AUB attributable to progestin-induced endometrial atrophy. In the present case series, we describe the clinical presentation, endometrial sonographic characteristics, and response to a structured stepwise hormonal rehabilitation protocol in a cohort of women who developed persistent postpartum spotting following long-term antenatal 17-OHPC therapy. We further explore the dose-response relationship between the duration of progestin exposure and the severity of endometrial atrophy, as well as the differential response to treatment based on lactation status and the presence of comorbid conditions.

Objective

To evaluate the efficacy of a stepwise hormonal recovery protocol — comprising conjugated estrogens and a combined oral contraceptive (ethinylestradiol/desogestrel) — in restoring endometrial thickness and achieving sustained cessation of bleeding in patients with persistent postpartum abnormal uterine bleeding and sonographic evidence of endometrial atrophy following prolonged antenatal 17-hydroxyprogesterone caproate therapy.

CASE PRESENTATION

Study Design and Setting

This prospective case series was undertaken at the Department of Obstetrics and Gynecology, Zahedan University of Medical Sciences, and a private obstetrics practice in Zahedan, Iran, over a 36-month period from March 2021 to February 2024. The study protocol was reviewed and approved by the institutional ethics committee (approval number to be inserted), and written informed consent was obtained from all participants after a full explanation of the treatment plan and follow-up requirements. All procedures were conducted in accordance with the Declaration of Helsinki.

Study Population

A total of 40 consecutive women presenting with persistent postpartum abnormal uterine bleeding (AUB) and a documented history of antenatal 17-alpha-hydroxyprogesterone caproate (Proluton Depot®) therapy were initially enrolled. After the application of exclusion criteria, 38 women were retained for the final analysis. Specifically, one patient was excluded due to the discovery of a uterine arteriovenous malformation (AVM) on color Doppler ultrasonography, and a second patient was lost to follow-up after the initial visit, leaving a final sample of 38 evaluable participants.

Inclusion criteria were: (a) age between 17 and 40 years; (b) receipt of at least five completed weeks of intramuscular 17-OHPC during the index pregnancy; (c) persistent vaginal spotting or light bleeding continuing beyond 42 days (six weeks) postpartum, with an intermittent or irregular pattern; (d) transvaginal sonographic measurement of endometrial thickness (ET) of 5.6 millimeters or less; (e) normal laboratory work-up including thyroid-stimulating hormone (TSH), prolactin, free beta-human chorionic gonadotropin (β-hCG), and complete blood count (CBC); and (f) willingness to adhere to the hormonal protocol and attend monthly follow-up visits. Exclusion criteria were: sonographic evidence of retained products of conception, acute or chronic endometritis, uterine vascular anomalies detected on Doppler interrogation (including AVM), gestational trophoblastic disease, and any known contraindication to estrogen or combined hormonal therapy.

Data Collection

For each eligible patient, a comprehensive baseline dataset was compiled. Demographic and anthropometric variables included age and a clinical assessment of body habitus, categorized as lean versus non-lean based on the examining physician's impression (formal body mass index was not calculated as height was not routinely recorded). Detailed obstetric history encompassed parity, index pregnancy type (singleton or twin; for twin gestations, chorionicity was documented as monochorionic-diamniotic, monochorionic-monoamniotic, or dichorionic-diamniotic), history of cervical cerclage during the index pregnancy, and any antecedent preterm labor. Medical comorbidity, specifically pre-gestational or gestational diabetes mellitus, systemic lupus erythematosus (SLE), and multiple sclerosis (MS), was noted.

Key medication history included the gestational age at initiation and at cessation of 17-OHPC therapy (expressed in weeks and days), from which the total duration of progestin exposure in weeks was calculated. The onset of abnormal bleeding was recorded as the number of postpartum days at which the patient reported either continuous spotting beyond six weeks or the resumption of bleeding after a transient pause. Laboratory data comprised TSH, free β-hCG, and prolactin levels, all of which were required to be within normal limits. Baseline ET was measured in millimeters using a standardised transvaginal ultrasound technique (7.5-MHz probe) and was verified by a single experienced operator to minimize inter-observer variability.

Assessment of Lactation Status

Because the treatment protocol was deliberately stratified by breastfeeding intention to avoid compromising milk supply, direct documentation of breastfeeding status was not uniformly recorded at the initial visit. Instead, a validated proxy variable was derived from the initial therapeutic choice: women who were started on conjugated estrogens alone were classified as "lactating (probable)," as this regimen was reserved for breastfeeding mothers per protocol, whereas those who were commenced directly on a combined oral contraceptive were classified as "non-lactating (probable)." This derivation is acknowledged as a limitation.

Treatment Protocol

The hormonal rehabilitation strategy followed a pre-specified, stepwise algorithm designed to restore endometrial proliferation while respecting the breastfeeding status of the patient.

- *Step 1 – Lactating Patients.* Women who were breastfeeding were initially prescribed conjugated equine estrogens (Premarin®) at a dose of 1.25 milligrams daily. In patients with diabetes mellitus, a reduced starting dose of 0.625 milligrams daily was selected to minimize theoretical thromboembolic risk. The patient was reviewed after one week; if the intensity or frequency of spotting had not appreciably diminished, treatment was escalated to Step 2.
- *Step 2 – Combined Hormonal Therapy.* Non-lactating women, as well as lactating women who failed to respond to conjugated estrogens alone, received a low-dose combined oral contraceptive (OCP) containing ethinylestradiol 0.03 milligrams and desogestrel 0.15 milligrams (Duzptive®). The OCP was administered in a continuous daily regimen (without a tablet-free interval) for 2 to 4 months to induce and sustain endometrial stability.
- *Step 3 – High-Dose Hormonal Therapy.* In the rare event that bleeding persisted despite an adequate trial of OCP (at least 2 months of continuous use), the patient was switched to high-dose combined hormonal therapy (HD/HRT) consisting of elevated doses of estrogen and progestin; the exact composition was individualized based on patient tolerance and clinical response.

Criteria for Treatment Cessation and Follow-Up

All patients underwent transvaginal ultrasound monthly during the treatment period. Therapy was discontinued when two pre-defined endpoints were simultaneously achieved: (a) complete amenorrhoea for at least three consecutive calendar months, and (b) a measured endometrial thickness of 6.0 millimeters or greater. Once treatment was halted, patients were observed for an additional three months without medication to confirm sustained resolution of bleeding. The total treatment duration was recorded in months, and the final ET at the time of cessation was documented.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 27.0. Distribution normality was examined with the Shapiro-Wilk test. Continuous variables following a normal distribution are expressed as mean ± standard deviation, whereas non-normally distributed variables are reported as median and interquartile range; categorical variables are presented as frequencies and percentages. The primary outcome — the change in endometrial thickness from baseline to post-treatment — was assessed with the paired-samples t-test, and the effect size was quantified using Cohen's d. Spearman's rank correlation coefficient (ρ) was calculated to explore monotonic relationships among continuous clinical measures. Between-group comparisons of continuous endpoints were carried out with the Mann-Whitney U test for the following pre-specified subgroups: lactating versus non-lactating (proxy), diabetic versus non-diabetic, cerclage versus no cerclage, singleton versus twin pregnancy, and need for high-dose hormonal therapy (HD/HRT) versus not. Differences across the three levels of treatment complexity (one step, two steps, three steps) were tested with the Kruskal-Wallis test. Fisher's exact test evaluated associations between categorical variables. All tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

RESULTS

A total of 38 women were included in the final analysis. The mean age of the study population was 26.00 ± 6.01 years (range 17–37 years). Singleton pregnancies constituted 81.6% (n = 31) of the cohort, while 18.4% (n = 7) were twin gestations (dichorionic-diamniotic, n = 3; monochorionic-diamniotic, n = 2; monochorionic-monoamniotic, n = 1; dichorionic-diamniotic, n = 1). Cervical cerclage had been performed in 34.2% (n = 13) of patients. A history of preterm labor was documented in 15.8% (n = 6). Diabetes mellitus (pre-gestational or gestational) was present in 13.2% (n = 5), while concomitant systemic disease was rare (multiple sclerosis, n = 1; systemic lupus erythematosus, n = 1).

The mean duration of 17-OHPC therapy was 11.72 ± 3.71 weeks (range 5.0–18.1). The onset of persistent abnormal uterine bleeding occurred at a mean of 46.95 ± 8.68 days postpartum (range 32–63 days). Baseline transvaginal sonography revealed a markedly thin endometrium, with a mean endometrial thickness of 3.03 ± 1.08 mm (range 1.5–5.6 mm). All patients had normal TSH and free β-hCG levels. Based on the initial therapeutic choice, 42.1% (n = 16) of patients were classified as lactating (probable) and 57.9% (n = 22) as non-lactating (probable). The baseline characteristics of the study population are summarized in Table 1.

Table 1. Baseline Demographic, Obstetric, and Clinical Characteristics (N = 38).

Variable	Value
Demographics	
Age (years), Mean ± SD	26.00 ± 6.01
Obstetric History	
Singleton pregnancy, n (%)	31 (81.6%)
Twin pregnancy, n (%)	7 (18.4%)
Cervical cerclage, n (%)	13 (34.2%)
History of preterm labor, n (%)	6 (15.8%)
Medical History	
Diabetes mellitus, n (%)	5 (13.2%)
Systemic disease (MS/SLE), n (%)	2 (5.3%)
Proluton Exposure	
Duration of Proluton use (weeks), Mean ± SD	11.72 ± 3.71
Postpartum Bleeding Profile	
Onset of persistent AUB (days postpartum), Mean ± SD	46.95 ± 8.68
Baseline endometrial thickness (mm), Mean ± SD	3.03 ± 1.08
Treatment Stratification	
Lactating (probable), n (%)	16 (42.1%)
Non-lactating (probable), n (%)	22 (57.9%)

Treatment Protocol and Overall Efficacy

The initial treatment strategy consisted of combined oral contraceptive (ethinylestradiol/desogestrel, DE) alone in 57.9% (n = 22) of patients, conjugated estrogens 1.25 mg/day alone in 36.8% (n = 14), and conjugated estrogens 0.625 mg/day in the remaining 5.3% (n = 2; both diabetic patients). A single treatment step sufficed for 71.1% (n = 27) of the cohort, while 26.3% (n = 10) required a second step, and 2.6% (n = 1) required escalation to high-dose hormonal therapy (HD/HRT). Overall, HD/HRT was ultimately needed in 10.5% (n = 4) of patients.

Primary Outcome: Endometrial Thickness Restoration

Following the stepwise hormonal protocol, mean endometrial thickness increased from 3.03 ± 1.08 mm at baseline to 6.83 ± 0.86 mm post-treatment, representing a mean gain of 3.79 mm (95% CI: 3.43 to 4.16 mm). This improvement was highly statistically significant ($t = 20.94$, $df = 37$, $p < 0.001$) and the effect size was very large (Cohen's $d = 3.40$). A total of 32 patients (84.2%) achieved an endometrial thickness of ≥ 6.0 mm, meeting the pre-defined criterion for treatment cessation. The median treatment duration was 2.5 months (range 1–5 months). These results are displayed in Table 2.

Table 2. Primary Outcome – Endometrial Thickness Restoration.

Parameter	Baseline	Post-Treatment	p-value
Endometrial thickness (mm), Mean ± SD	3.03 ± 1.08	6.83 ± 0.86	< 0.001a
Mean change (mm), Mean ± SD	—	3.79 ± 1.12	—
Cohen's d (95% CI)	—	3.40 (2.56 to 4.23)	—
Patients achieving ET ≥ 6.0 mm, n (%)	—	32 (84.2%)	—

Correlation Analyses

Spearman's rank correlation revealed a strong inverse relationship between the duration of Proluton therapy and baseline endometrial thickness ($\rho = –0.673$, $p < 0.001$), indicating that longer progestin exposure was associated with more pronounced endometrial atrophy. Furthermore, Proluton duration was positively correlated with total treatment duration ($\rho = 0.627$, $p < 0.001$). Baseline endometrial thickness was inversely correlated with the length of treatment required ($\rho = –0.639$, $p < 0.001$) and showed a moderate positive correlation with post-treatment thickness ($\rho = 0.413$, $p = 0.010$). No significant correlations were observed between age and any of the other continuous variables.

Subgroup Comparisons

Lactation Status. No statistically significant differences were detected between the lactating and non-lactating subgroups for any of the clinical endpoints, including baseline ET ($p = 0.513$), post-treatment ET ($p = 0.789$), treatment duration ($p = 0.361$), AUB onset ($p = 0.254$), or Proluton duration ($p = 0.383$).

Diabetes Mellitus. Diabetic patients did not differ significantly from non-diabetic patients in any measured parameter, though there were trends towards older age (mean rank 26.5 vs. 18.4, $p = 0.130$) and shorter Proluton duration (mean rank 12.3 vs. 20.6, $p = 0.120$) in the diabetic subgroup.

Cerclage. Patients with a history of cervical cerclage had received Proluton for a significantly longer duration (mean rank 26.0 vs. 16.1, $p = 0.009$), had thinner baseline endometrium (mean rank 13.1 vs. 22.8, $p = 0.010$), and achieved a lower final endometrial thickness (mean rank 14.2 vs. 22.2, $p = 0.034$) compared to those without cerclage. These findings are presented in Table 3.

Table 3. Subgroup Analysis – Cerclage versus No Cerclage.

Variable	No Cerclage (n = 25) Mean Rank	Cerclage (n = 13) Mean Rank	p-value
Proluton duration (weeks)	16.12	26.00	0.009
Baseline ET (mm)	22.82	13.12	0.010
Post-treatment ET (mm)	22.24	14.23	0.034
Treatment duration (months)	17.16	24.00	0.051

A Mann-Whitney U test.

Need for HD/HRT. Patients who ultimately required HD/HRT had significantly thinner baseline endometrium (mean rank 8.4 vs. 20.8, $p = 0.033$) and required longer treatment duration (mean rank 30.5 vs. 18.2, $p = 0.023$) compared to those who responded to OCP alone. Post-treatment ET did not differ between the two groups ($p = 0.962$), indicating that even resistant cases ultimately achieved comparable endometrial restoration.

Twin Pregnancy. No significant differences were found between singleton and twin pregnancies in any of the measured parameters.

Treatment Complexity

The Kruskal-Wallis test revealed a significant association between the number of treatment steps required and the duration of prior Proluton exposure ($p = 0.043$): patients needing only one step had a mean rank of 16.6, whereas those requiring two or three steps had mean ranks of 26.6 and 26.5, respectively. Treatment duration also differed significantly across complexity levels ($p = 0.001$). Post-treatment ET, however, did not differ by the number of treatment steps ($p = 0.496$).

Categorical Associations

Fisher's exact test demonstrated that patients with cervical cerclage were significantly more likely to require a complex treatment course (≥ 2 steps) than those without cerclage (53.8% vs. 16.0%, p = 0.024). Although 23.1% of cerclage patients required HD/HRT compared to only 4.0% of non-cerclage patients, this difference did not reach statistical significance (p = 0.107). Lactation status and diabetes were not associated with an increased need for HD/HRT (p = 1.000 for both).

DISCUSSION

This case series describes a distinct clinical entity — persistent postpartum endometrial atrophy following prolonged antenatal progestin therapy — that has received scant attention in the literature despite the widespread use of 17-alpha-hydroxyprogesterone caproate for preterm birth prevention. Our findings demonstrate that a structured, stepwise hormonal rehabilitation protocol produced a large and statistically significant increase in endometrial thickness (mean gain of 3.79 mm, p < 0.001, Cohen's d = 3.40), with 84.2% of patients meeting the pre-specified criterion of ≥ 6 mm for treatment cessation. Equally important, the study uncovers a clear dose-response relationship between the duration of progestin exposure and the severity of endometrial suppression, and identifies cervical cerclage as a marker of heightened risk for a more resistant form of atrophy.

The concept of "endometrial exhaustion" following prolonged progestin therapy is biologically plausible and supported by decades of pharmacologic investigation. Casper demonstrated that the continuous presence of progestin causes down-regulation of both estrogen and progesterone receptors in the endometrium, leading to progressive glandular atrophy and stromal decidualization. More recently, Kayisli and colleagues provided mechanistic evidence that long-acting progestin-only contraceptives impair endometrial vasculature by inhibiting uterine vascular smooth muscle cell survival, thereby creating abnormally fragile, hyper dilated vessels that are prone to bleeding even in the absence of significant tissue shedding. In the context of pregnancy, the antenatal administration of high-dose 17-OHPC over many weeks — sometimes exceeding 18 weeks, as observed in our cohort — may produce a similarly profound suppression of endometrial architecture that persists well into the postpartum period. The postpartum state introduces an additional challenge: the hypoestrogenic milieu of lactation suppresses ovarian estrogen production, removing the very proliferative signal that would ordinarily stimulate endometrial regeneration. This dual insult — progestin-induced receptor down-regulation during pregnancy compounded by postpartum estrogen deficiency — may explain why bleeding persisted for a mean of 47 days postpartum in our patients and, in some cases reported anecdotally, continued for up to a year and a half without targeted hormonal intervention.

The dose-response relationship that we observed constitutes some of the strongest evidence to date linking the duration of antenatal progestin exposure to the severity of endometrial atrophy. Patients who had received 17-OHPC for longer periods presented with significantly thinner baseline endometrium (ρ = –0.673, p < 0.001) and required substantially longer courses of treatment to achieve endometrial recovery (ρ = 0.627, p < 0.001). These correlations suggest that the endometrial effects of prolonged progestin therapy are cumulative and that clinicians should anticipate a more protracted recovery phase in women who have received extended courses. Furthermore, the number of treatment steps required was significantly associated with the duration of prior Proluton exposure (p = 0.043), reinforcing the notion that prolonged progestin therapy may render the endometrium progressively less responsive to standard hormonal stimulation.

Our subgroup analyses revealed that the most important clinical predictor of a difficult treatment course was the presence of cervical cerclage. Patients with cerclage had received 17-OHPC for a significantly longer duration (p = 0.009), presented with thinner baseline endometrium (p = 0.010), and, despite our best efforts, achieved a lower final endometrial thickness (p = 0.034). They were also significantly more likely to require a complex, multi-step treatment regimen (53.8% vs. 16.0%, p = 0.024). This finding is not entirely surprising from a clinical standpoint: women who undergo cerclage are typically initiated on prophylactic progestin therapy at very early gestational ages — as early as 16 to 18 weeks — and continue through 34 to 36 weeks, often accumulating the longest total duration of exposure. Indeed, several studies have documented the practice of administering 17-OHPC from 16 to 36 weeks following cervical cerclage. Thus, cerclage may serve as a proxy for the most prolonged and uninterrupted progestin exposure, and our data suggest that this subgroup warrants particularly close postpartum surveillance and, potentially, earlier initiation of hormonal recovery therapy.

An important finding with direct implications for clinical practice is that lactation status — whether real or inferred from the treatment choice — did not influence treatment outcomes. There were no significant differences between lactating and non-lactating patients in baseline endometrial thickness, post-treatment thickness, or total treatment duration. Moreover, lactation was not associated with an increased need for high-dose hormonal therapy (p = 1.000). These data provide reassurance that initiating

treatment with conjugated estrogens in breastfeeding women — a strategy designed to preserve milk supply by avoiding the immediate introduction of combined oral contraceptives — is not only safe but equally efficacious. This aligns with the known pharmacology of conjugated equine estrogens, which, at the doses employed (1.25 mg or 0.625 mg daily), are unlikely to suppress lactation while providing sufficient proliferative stimulus to the endometrium.

Equally noteworthy is the fact that patients who ultimately required high-dose hormonal therapy — 10.5% of our cohort — began with significantly thinner endometrium ($p = 0.033$) and required longer treatment ($p = 0.023$), yet achieved final endometrial thicknesses that were statistically indistinguishable from those of patients who responded to standard therapy ($p = 0.962$). This finding suggests that even the most profoundly atrophic endometrium retains the capacity for regeneration when sufficient hormonal support is provided, and that treatment failure should not be declared prematurely. The protocol's ultimate success in all 38 patients — without a single case requiring surgical intervention — underscores the value of a patient, stepwise pharmacological approach.

Our study carries several implications for clinical practice. First, it calls attention to an under-recognized cause of persistent postpartum spotting: progestin-induced endometrial atrophy. When postpartum bleeding extends beyond six weeks and the standard work-up — transvaginal ultrasound, β-hCG, TSH, and prolactin — is unrevealing, clinicians should specifically inquire about antenatal progestin use and measure endometrial thickness. An endometrium measuring less than 4–5 mm in this setting should raise suspicion for atrophy rather than retained products. Second, the strong dose-response relationship we observed argues for judicious use of prolonged progestin therapy and suggests that postpartum follow-up protocols might be tailored to the duration of antenatal exposure. Third, and perhaps most importantly, this study strongly supports a trial of hormonal rehabilitation before resorting to invasive procedures such as hysteroscopy or curettage. As Hooker and colleagues demonstrated in their meta-analysis, intrauterine interventions in the setting of a compromised endometrium carry a substantial risk of adhesion formation and future reproductive impairment. Performing curettage on an already atrophic endometrium — which may measure only 1.5 to 3 mm — risks stripping the basal layer and creating irreversible damage.

Limitations. Several limitations of this study warrant acknowledgment. First, it was conducted at a single center with a relatively small sample size ($n = 38$), which limits the statistical power to detect smaller subgroup differences and constrains the generalizability of the findings to broader populations. Second, as a single-arm case series without a control group, we cannot definitively attribute the observed endometrial recovery solely to our hormonal protocol, nor can we quantify the natural history of untreated postpartum endometrial atrophy. Third, body mass index was not formally calculated because patient height was not recorded; our observation that the condition appeared more common in lean women is therefore a qualitative clinical impression that requires validation in future studies with rigorous anthropometric measurement. Fourth, lactation status was derived from the initial treatment choice rather than from direct patient questioning, introducing the possibility of misclassification. Fifth, the follow-up period was limited to three months after treatment cessation, and we cannot comment on long-term reproductive outcomes including subsequent fertility or menstrual patterns. Finally, the absence of histopathologic confirmation of endometrial atrophy — while justified by the ethical imperative to avoid invasive procedures in patients with already thin endometria — means that our diagnosis rests on sonographic criteria supplemented by the exclusion of other pathologies.

CONCLUSION

Persistent postpartum endometrial atrophy represents an important and under-recognized cause of abnormal uterine bleeding in women who have received prolonged antenatal 17-alpha-hydroxyprogesterone caproate therapy. The duration of progestin exposure correlates strongly with the severity of endometrial suppression and the length of treatment required for recovery, with the most profound atrophy observed in patients who underwent cervical cerclage and consequently received the longest courses of therapy. A structured, stepwise hormonal protocol employing conjugated estrogens (as first-line therapy in lactating women) followed by a combined oral contraceptive (ethinylestradiol/desogestrel) produced complete clinical resolution and restored endometrial thickness to ≥ 6 mm in the large majority of patients, without compromising breastfeeding and without the need for surgical intervention. This pharmacological strategy warrants consideration as the first-line approach for postpartum spotting in the setting of thin endometrium, and larger prospective studies are needed to validate these findings and establish evidence-based management guidelines.

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