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Research Article

Duration-Dependent Histomorphological Alterations in Human Endometrium Following Progestin Therapy: Evidence from a Tertiary Care Center

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ABSTRACT

Objective: This research will assess the time varying histologic alterations in human endometrium during progestin therapy at a tertiary care hospital.
Materials and Methods: A retrospective observational study was at multiple tertiary care centers, in a span of three years. A total of 240 women who received progestin therapy as an indicator of different gynecological conditions were used as the sample on endometrial biopsy. The patients were stratified into four groups according to the duration of therapy: Group A (less than 3 months), Group B (3 -6 months), Group C (6 - 12 months) and Group D (more than 12 months). Blinded pathologists scored the histological parameters such as glandular atrophy, stromal decidualization, pseudosarcomatous changes and inflammatory infiltrate. ANOVA and Chi -square tests were used to conduct the statistical analysis.

Results: There were significant variations with time in all groups. Group A had a minimum of glandular atrophy (15%), whereas in Group D, the glandular atrop hy was mostly present (88.3, $p<0.001$). Group B (91.7) had the highest level of Stromal decidualization followed by a slow reduction in long -time treatment. Group C and D were the only groups with pseudosarcomatous stromal changes ($p=0.002$). The total histological score suggested that there was a progressive change in the morphology of the secretory to atrophic with the length of treatment ($p<0.05$).

Conclusion: Progestin treatment has specific time-contingent histomorphological changes on the endometrium. Short-term therapy is typified by decidualization, whereas the long-term exposure causes extensive atrophy in the glands and may cause stromal metaplasia. These temporal trends are critical in the process of diagnosing malignancy by pathologists to prevent a misdiagnosis of malignancy and to detect therapeutic outcomes by clinicians.

Keywords: Endometrium, Progestin Therapy, Histomorphology, Glandular Atrophy.

INTRODUCTION

The human endometrium is a motile mucosal lining which experiences cyclic regeneration, differentiation and shedding by highly controlled ovarian steroid
hormones, mainly estrogen and progesterone [1]. The implantation of the embryo and the process of early pregnancy maintenance are impossible without this physiological reorganization and regulated by a complex of hormonal signals and local growth factors [2]. The proliferative phase is mediated by estrogen leading to the multiplication of the epithelial cells, followed by the secretory phase that is mediated by progesterone
and prepares the stroma to be decidualized [3]. The natural hormonal balance is, however, therapeutically manipulated in a number of pathological states, such as abnormal uterine bleeding (AUB), endometrial hyperplasia and as part of hormone replacement therapy (HRT) or birth control [4]. The basis of such therapeutic interventions is progestins,

which are synthetic analogs of progesterone and have strong antiprolliferative actions against the estrogen-primed endometrium [5]. Although their clinical application is widespread, precise histomorphological development of the endometrium to different lengths of progestin stimulation continues to be a topic of intense pathological as well as clinical knowledge [6].

Mechanism of action The progestins act on intracellular progesterone receptors (PR) of which PR -A and PR -B are isoforms [7]. When the receptor complex binds to the ligand, it is translocated to the nucleus, which is a transcription factor and alters gene expression [8]. The effect is the downregulation of estrogen receptors (ER), mitotic inhibition and stromal decidualization [9]. In particular, progestins inhibit cyclins expression and enhance the expression of cell cycle inhibitors like p21, thus halting the glandular growth [10]. Although the molecular pathways are well-illustrated, how these molecular events are translated into physical histological structure with time is complicated. The first research by Noyes et al. set the precedent in dating the endometrium but the requirements relied on natural cycles [11]. Perturbation of exogenous progestins alters this synchrony, forming a histological scenario, which may even resemble pathological ones unless viewed within the framework of therapeutic history [12].

As a treatment, progestins can be used in a range of different forms, such as oral micronized progesterone, synthetic progestins such as medroxyprogesterone acetate (MPA), levonorgestrel-releasing intrauterine systems (LNG-IUS), and depot injections [13]. These agents vary in terms of their potency, bioavailability and the local concentration [14]. As an example, LNG-IUS provides large local levels of levonorgestrel that targets the endometrial tissue, and in many cases, leads to more significant atrophic alterations than oral regimens [15]. Yet, despite the mode of delivery, the time aspect of exposure is a very important variable. Acute bleeding will have short -term therapy prescribed, but long-term therapy will be prescribed at the reversal of hyperplasia or chronic management of endometriosis [16].

The histological reaction to progestins is dynamic; it changes. During early stages of therapy, endometrium generally has characteristics of extreme secretory shift and stromal decisionalization [17]. It is a physiological condition that is simulating the pre-menstrual period of a natural cycle but is maintained by the exogenous hormone [18]. During the course of the therapy, the glandular epithelial suppressive effect is exacerbated. Glands become inactive, cystic, atrophic and stroma may experience fibrosis [19]. But this has paradoxical changes as well, when exposed to it over time. Cases of stromal metaplasia or even pseudosarcomatous alterations in response to long-term progestin use are documented and can be disastrous to the unsuspecting pathologist and could be incorrectly diagnosed as stromal sarcoma or carcinosarcoma [20].

This diagnostic problem supports the need to have a comprehensive description of duration-dependent histomorphology. Failed interpretation of the effects of progestin may result into unnecessary surgery, including hysterectomy, by women undergoing fertility preservation procedure or who are undergoing conservative management [21]. On the other hand, the inability to differentiate persistent hyperplasia in the presence of progestin induced atrophy would delay the detection of underlying malignancy [22]. The World Health Organization (WHO) classification of female reproductive tumors is recognized as acknowledging the effects of hormone therapy but does not provide any concrete granular recommendations on the timely course of the change [23]. Moreover, there is the variation in individual response, which makes it even more complex. Body mass index (BMI), age, concomitant medications, and the purpose of therapy (e.g., contraception vs. treatment of hyperplasia) are some of the factors that affect the endometrial milieu [24].

Obesity is peripheral aromatization of androgens into estrogens that produces a hyperestrogenic environment capable of cancelling the antiproliferative action of progestins and this can change the histological order [25]. Likewise, perimenopausal women whose endogenous hormone concentrations are irregularly distributed can display a divergent histological image than the premenopausal women using contraceptives [26].

Although the clinical prevalence of progestin treatment is quite high, a small number of large -scale investigations systematically classify endometrial histology according to the duration of exposure alone [27]. Majority of available literature emphasizes the effectiveness of the drug in curing hyperplasia as opposed to the descriptive pathology of the intermediate conditions [28]. Certain studies have also pointed out the pill effect in those taking oral contraceptives, which include dormant glands and compressed stroma, yet have failed to cover the range of changes observed in therapeutic doses applied in bleeding disorders or in the regression of hyperplasia [29]. Moreover, there is a new generation of progestins with different androgenic and glucocorticoid activity that require a reassessment of their effects on the tissues [30].

Regarding the public health, such changes are essential to comprehend in tertiary care facilities to which the complicated cases are referred [31]. Pathologists in such institutions regularly deal with biopsies in patients with ambiguous hormonal histories [32]. Having a solid construct that can associate the period of treatment with certain histological indicators can be used as a diagnostic tool. An example is when a biopsy depicts deep decidualization with no atrophy, this may indicate the recent commencement of therapy, but diffuse atrophy with stromal hyalinization may indicate long-term compliance [33]. The correlation may also be used as a surrogate of patient compliance in clinical trials or therapeutic monitoring [34].

MATERIALS AND METHODS

Study Design and Setting: This is a retrospective observational study which was carried out at the Department of Pathology in cooperation with the Department of Obstetrics and Gynecology at multiple tertiary care centers. The research was conducted during the period between January 2022 and December 2024. Study Population The study population was composed of women aged between 18 and 50 years who had been in progestin therapy and did endometrial biopsy. The initial screening of medical records was conducted on 350 medical records. Inclusion criteria were: (1) History of at least 4weeks of progestin therapy (oral, injectable, or intrauterine) before biopsy; (2) Availability of sufficient clinical records that included the type of progestin, dosage and precise duration of progestin therapy; (3) Adequate endometrial tissue sample to undergo histological examination. These were the exclusion criteria: (1) A history of endometrial carcinoma or complex hyperplasia with atypia before starting therapy; (2) An Existing intrauterine devices other than LNG-IUS (3) ; (4) Pregnancy or lactation during the period of biopsy. Group A (Short- term): Period less than 3 months (n=60). Normally used in the treatment of acute bleeding. Group B (Medium-term): 3- 6 months (n=60). Commonly applied to initial hyperplasia treatment. Group C (Long -term): Duration 6 -12 months (n=60).Maintenanceorsecondary hyperplasia remission. Group D (Prolonged): Time =12 months days and above (n=60). Intrauterine (long - term) contraception or chronic management AUB. Data Collection Clinical Data that was extracted were age, parity, BMI, indication of therapy (AUB, hyperplasia without atypia, contraception, endometriosis), type of progestin that was administered (e.g., Medroxyprogesterone acetate, Norethisterone, Levonorgestrel), and route of administration. The menstrual history such as the date of last menstrual period relative to the biopsy was used to explain the cycle phase but progestin therapy commonly results in amenorrhea.Glandular Atrophy Score: 0

(None), 1 (Mild, < 25 % glands), 2 (Moderate, 25 -50%), 3 (Severe, >50%).
Stromal Decidualization: This is characterized by large polygonal stromal cells which have excessive eosinophilic cytoplasm. Rated as Absent, Focal or Diffuse. Statistical Analysis
Data were put in a secure database and processed with SPSS version 26.0. The continuous
variables (e.g., age, BMI) were represented in the form of mean SD and compared with the help of One -way Analysis of Variance (ANOVA). Categorical
variables (e.g. histological grades, presence of atrophy) were then presented as frequencies and percentages and compared by use of Chi-square test or Fishers exact test where necessary. A p-value below 0.05 was taken to be of a statistical significance. The inter-observer agreement of histological scoring was computed by the use of Cohens Kappa coefficient. The power analysis showed that a sample of 240 would give 90% power in identifying a medium effect size in the difference between histological scores between the four groups.

RESULTS

Demographic and Clinical Characteristics 240 patients that fit the inclusion criteria were included in the final study. The average age of the study sample was 34.5 +- 6.2 years. The observed differences in histology were not found to be statistically significant in terms of age, BMI or parity among the four duration groups, making it clear that the observed differences were due to therapy duration and not due to demographic confounding factors. The overall experience of Abnormal Uterine

Bleeding (45%), Endometrial Hyperplasia without atypia (30%), and Contraception (25%) was the most common indication of the therapy. The most frequent means of delivery was
Urethane-releasing levonorgestrel intrauterine delivery (50%), then came oral progestins (40) and injections (10%).

Table 1: Demographic and Clinical Characteristics of Study Participants (N=240)

Characteristic	Group A (<3 mo)	Group B (3-6 mo)	Group C (6-12 mo)	Group D (>12 mo)	P-value
Mean Age (years)	33.8 ± 5.9	34.2 ± 6.1	35.0 ± 6.5	34.9 ± 6.3	0.654
Mean BMI (kg/ m²)	26.4 ± 3.2	27.1 ± 3.5	26.8 ± 3.4	27.3 ± 3.6	0.512
Parity (Nulliparous %)	35.0%	33.3%	36.7%	34.2%	0.945
Indication: AUB (%)	50.0%	45.0%	43.3%	41.7%	0.721
Indication: Hyperplasia (%)	25.0%	30.0%	31.7%	33.3%	0.689
Route: LNG-IUS (%)	45.0%	50.0%	51.7%	53.3%	0.810

Table 2: Glandular Morphological Changes across Duration Groups

Glandular Feature	Group A (n=60)	Group B (n=60)	Group C (n=60)		P-value
Secretory Activity	55 (91.7%)	40 (66.7%)	20 (33.3%)		<0.001
Glandular Atrophy (Severe)	2 (3.3%)	10 (16.7%)	35 (58.3%)		<0.001
Cystic Dilation		15 (25.0%)		30 (50.0%)	0.003
Mitotic Figures (High)	30 (50.0%)	15 (25.0%)	5 (8.3%)	2 (3.3%)	<0.001
Inactive Glands	3 (5.0%)	10 (16.7%)	40 (66.7%)		<0.001

Statistically Significant ($p < 0.05$)

Table 3: Stromal Alterations and Decidualization Scores

Stromal Feature	Group A (n=60)	Group B (n=60)	Group C (n=60)	Group D (n=60)	P-value
Decidualization (Diffuse)	15 (25.0%)	55 (91.7%)	30 (50.0%)	10 (16.7%)	<0.001
Stromal Cellularity (High)	40 (66.7%)	35 (58.3%)	20 (33.3%)	10 (16.7%)	<0.001

Stromal Fibrosis	5 (8.3%)	10 (16.7%)	25 (41.7%)	45 (75.0%)	<0.001
Pseudosarcomatous Change	0 (0.0%)	0 (0.0%)	5(8.3%)	9 (15.0%)	0.002
Edema	20 (33.3%)	25 (41.7%)	10 (16.7%)	5(8.3%)	0.004

Statistically Significant ($p < 0.05$)

Table 4: Inflammatory and Vascular Changes

Feature	Group A (n=60)	Group B (n=60)	Group C (n=60)	Group D (n=60)	P-value
Chronic Endometritis	8 (13.3%)	10 (16.7%)	12 (20.0%)	15 (25.0%)	0.450
Acute Inflammation	5 (8.3%)	3 (5.0%)	2(3.3%)	1(1.7%)	0.312
Vascular Thrombosis	2 (3.3%)	5 (8.3%)	8 (13.3%)	12 (20.0%)	0.041
Spiral Artery Development	45 (75.0%)	30 (50.0%)	15 (25.0%)	10 (16.7%)	<0.001
Breakthrough Bleeding Histology	25 (41.7%)	15 (25.0%)	10 (16.7%)	8 (13.3%)	0.018

Statistically Significant ($p < 0.05$)

Table 5: Overall Histological Scoring and Inter - observer Agreement

Parameter	Group A Mean Score	Group B Mean Score	Group C Mean Score	Group D Mean Score	P-value (ANOVA)
Atrophy Score (0-3)	0.4 ± 0.5	1.2 ± 0.6	2.3 ± 0.7	2.8 ± 0.4	<0.001
Decidualization Score (0-3)	1.1 ± 0.6	2.7 ± 0.5	1.8 ± 0.8	0.9 ± 0.6	<0.001
Ki-67 Index (%)	12.5 ± 3.2	8.4 ± 2.1	4.2 ± 1.5	2.1 ± 1.0	<0.001
Cohen's Kappa (Agreement)	0.85	0.88	0.82	0.86	N/A
Diagnostic Confidence	High	High	Moderate	High	N/A

Statistically Significant ($p < 0.05$)

Histomorphological Interpretation The histological observation was found to have a distinct development of morphological alterations involving the length of progestin exposure. Group A (<3 months) had mostly endometrial features of an active secretory change and an early stromal decidualization. Atrophy in the glands was small. With the time developing to Group B (3 -6 months), stromal decidualizationwent diffuse and maximal, with the glandular activity starting to decline. A transition period was seen in Group C (6 -12 months) in which there was a regression in decudialization and moderate to severe atrophy in the gland. At Group D (>12 months), the endometrium had been atrophic, with

inactive, thin glands, and fibrotic hypocellular stroma. It is also important to note that the pseudosarcomatous stromal changes were not observed in the short period groups but in 15% of the long-term therapy. These results were reflected in the proliferation index (Ki-67) whose group A had a substantial reduction in Group D.

DISCUSSION

The current research offers an in-depth discussion of the time-related histomorphological changes in the human endometrium after the administration of progestin. The present results support our hypothesis that the progesterone driven changes are not static, but dynamically changing with time, shifting to a secretory-decidual stage to a terminal atrophic-fibrotic stage [1]. This time stratification is essential in proper pathological diagnosis and clinical treatment [2].

The initial stage of treatment (Group A, <3 months) was marked with incessant secretory action and the development of stromal decadentization. This is in line with the classical perception of progesterone action in which the hormone causes stabilization of the

endometrium and prompts differentiation [3]. According to Ferenczy et al., the thin endometrium

and decidualized stroma frequently appear in the pill effect of the oral contraceptives [4]. In our study, however, this is differentiated as compared to therapeutic use of progestin in bleeding disorders. The high mitotic index in 50 percent of cases in Group A, indicates that the glandular epithelium had not been completely inhibited by the antiprolliferative effect [5]. This is clinically pertinent; the biopsies performed in this interval under monitoring of hyperplasia may result in false-negative outcomes in terms of the regression, since the glands can be still active even in the presence of the stromal changes [6].

The highest stromal decidualization was seen in Group B (3-6 months) and this is the apogee of the influence of progestin on stromal compartment. A typical feature of progesterone exposure is the process of decidualization of fibroblast-like stromal cells into larger glycogen - filled decidual cells [7]. In this group, we had 91.7% diffuse decidualization, which was very high compared to the prolonged therapy. This observation is in line with other researchers, including Silverberg et al., who observed that (decidualization) is usually the most evident before deep atrophy attack occurs [8]. This clinical implication is that diffuse decidualization with no atrophy on biopsy is probably an indication of adherence to the treatment over a medium period [9]. In case a patient reports a long-term use and presents such a pattern, non- compliance or malabsorption is to be suspected [10].

The main results of our research are the gradual progression of glandular atrophy with length. Group D (>12 months) showed 88.3 per cent severe glandular atrophy in patients. This makes the long-term effectiveness of progestins to inhibit endometrial proliferation, which is the treatment objective in the management of hyperplasia, a fact [11]. It is a mechanism of downregulating estrogen receptors and directly inhibiting the production of the DNA in the glandular cells [12]. Nonetheless, the observation of cystic dilation in half of the samples of Group D needs considering. Cystic atrophy is a nonmalignant problem, which is commonly observed in postmenopausal women or women under long term progestin combination, where the glandular outlets are blocked by stromal fibrosis [13]. Pathologists should also not confuse it with cystic hyperplasia; absence of cellular crowding and low mitotic activity is the main distinguishing factor, which is also validated by our Ki-67 data that decreased to 2.1% in Group D [14].

Group C and D also involve the development of pseudosarcomatous changes in the stroma which are of special diagnostic interest. These were bizarre, hyperchromatic, stromal nuclei alterations, which had not been seen in short-term treatment but were found in 15% of the extended sample [15]. This can be referred to as progestin- associated stromal decidualization with atypia and mimics endometrial stromal sarcoma [16]. According to literature by Oliva et al. these changes are benign and they in turn recede when the therapy is stopped [17]. This is supported by our data, these changes only being observed within the diffuse atrophy and low mitotic indices context [18]. These cases can be wrongly diagnosed and treated as malignancy and thus subjected to unnecessary hysterectomies [19]. Thus, our research highlights that pathologists should inquire about the progestin history in the presence of atypical stromal cells on atrophic background [20].

The vascular alterations were also duration dependent. There is a loss in spiral artery development which is characteristic of secretory phase [21]. On the other hand, vascular thrombosis was higher in the protracted group. This can be associated with the hemostatic influence of high- concentration progestins on the local effect, especially in LNG-IUS [22]. Although this histological evidence did not result in clinical ischemia in our cohort, it contributes to the picture of the long-term tissue remodeling [23]. The decreasing tendency on the breakthrough bleeding histology in Group A to Group D is linked to clinical

reports that the tendencies of bleeding stabilize after 6 months of progestin treatment [24].

The atrophy timeline is comparable to the current literature on LNG-IUS, which found that atrophy was substantial after 6 months [25]. But our analysis contains both oral and injectable progestins implying that effect of the duration is a class effect on progestins even though with diverse magnitudes [26]. The Ki-67 proliferation index was an objective measure that was used to verify our

morphological scoring [27]. The quantitative data of atrophy is the sharp drop of 12.5% to 2.1% in Group A to Group D respectively [28]. This justifies the usefulness of IHC as an adjunct in tricky situations in which morphological atrophy is inconclusive [29].

Decremerents of this research are that it is a retrospective study which depends on the accuracy of reported therapy duration by patients [30]. Furthermore, although we made an adjustment in progestin type, the different strengths of different synthetic progestins can be heterogenous [31]. Such timelines need improvement in future prospective studies that have standardized dosing [32]. In addition, we failed to follow up on whether these changes were reversible once we stopped, and this is a significant aspect on fertility preservation counseling [33].

In spite of these shortcomings, the advantages of this study are the huge sample size of a tertiary care facility and the fact that the assessment was conducted blindly by a group of pathologists [34]. The inter -observer agreement is high (Kappa-0.8 and above), as the histological scoring system used is reproducible [35]. The strength of the association that varies over time is supported by the statistical significance ($p < 0.05$) of the main parameters [36].

CONCLUSION

The secretory activity and early decidualization are seen during the short-term therapy (<3 months), whereas
the peak stromal decidualization is observed in the medium-term therapy (36 months). Its long-term exposure (>12 months) causes severe atrophy of the glands, stromal fibrosis and
sometimes pseudosarcomatous alteration.Clinicians would need to view the 6 -month point as an important milestone to evaluate the therapeutic efficacy of histology in the treatment of hyperplasia. Research in the future must be aimed on reversibility of such changes and molecular markers that predict the individual variability in response.

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