Low-risk endometrial hyperplasia: hysteroscopy and histologic evaluation after treatment with LH-RH analogue

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Summary: Endometrial hyperplasia is an endometrial pathologic condition often found at perimenopausal age. Abnormal uterine bleeding (A.U.B.) is the most frequent symptom of endometrial hyperplasia. The combination of hysteroscopy and endometrial biopsy is the most suitable approach for the diagnosis of endometrial hyperplasia in symptomatic patients.

We have studied endometrial modifications due to LHRH-analogue in 75 patients with AUB and with a hysteroscopic and histologic picture of low-risk endometrial hyperplasia.

LHRH analogue is a valid treatment for all estrogen induced pathologies, because of its suppressive action on hypothalamic-hypophysary gonadotropins.

The administration of LHRH for 4 months induced an improvement of the menstrual cycle within the first month of treatment in 53.3% of cases. At the end of treatment 100% of the patients were in amenorrhea. The hysteroscopic follow-up at 3 months showed an endometrial thinning with a tendency to hypoatrophy of the mucosa in 72% of cases. Three months after the end of treatment 20 patient had regular menstrual cycles and hysteroscopic and a histologic picture of normal endometrium. Only 30 patients had persistent amenorrhea with a consequent hysteroscopic and histologic picture of endometrial hypoatrophy. The use of LHRH analogue seems to have a great impact on the management of estrogen-dependent gynaecological benign diseases.

Key words: Abnormal uterine bleeding; Endometrial inhibition; LH-RH analogue; Hysteroscopic diagnosis.

INTRODUCTION

Glandular hyperplasia of the endometrium is a pathological condition, caused by absolute or relative hyperestrinism, which occurs more frequently around menopause and less frequently during the fertile age. The clinical interest here arises not only from the risk of neoplastic transformation but also from the possible onset of serious problems of anaemia. The symptom is usually A.U.B. (Abnormal Uterine Bleeding).

The oncogenic risk varies form 0,4 to 3% in low-risk endometrial hyperplasia up to 8% in cases considered at high risk, with a progression time towards carcinoma of about 10 years in the first case and 4 to 5 years in the second ([1, 2, 3]).

According to the most recent literature, Kurman ([2]), Ferenczy ([4]), and to the recent proposal of classification published

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by the International Society of Gynaecological Pathologists (I.S.G.P.) under the auspices of the W.H.O. ([5]), hyperplasia can be classified in two categories, as follows:

1) *Endometrial Hyperplasia (E.H.)* (Simple glandular hyperplasia - Cystic glandular hyperplasia - Adenomatous glandular hyperplasia), the simple and complex forms with no cytological atypisms;

2) *Endometrial Intraepithelial Neoplasia (E.I.N.)*: characterized by cytological alterations. The latter can be considered a precursor of endometrial carcinoma, with a transformation risk of 5-12% within an average period of 5 years.

Only 2% of patients with endometrial hyperplasia without atypisms and with a much longer natural history, progress into carcinoma, the various forms of *Endometrial Hyperplasia* are therefore biologically benign and not related to adenocarcinoma ([1, 4]).

By providing a direct view of the uterine cavity, hysteroscopy shows itself as the best diagnostic means in cases of abnormal uterine bleeding.

The advantages are:

— a panoramic view with topographic map of the lesion;

— codification of specific morphological parameters for the selection of different pathologic areas at risk;

— the possibility of target endometrial sampling.

This method is carried out at ambulatory level, with no traumas and can therefore be repeated.

The combination of hysteroscopy examination and endometrial biopsy provides good diagnostic accuracy, progressing from low risk (73%) to higher risk forms (high-risk E.I.N. 85.5%, Ca 97.8%) ([6]).

Of all the drugs most commonly administered for the treatment of such conditions, mention should be made of the most frequently prescribed group namely progestins. Of equal interest is the use of IUDs treated with progesterone ([7]). The effectiveness of taking the pill in conjunction with the above has also been demonstrated ([8]). Danazol is a further effective treatment although its side effects rule out a prolonged use.

The aim of our work has been to test the effectiveness of treatment using GnRH Analogues on low risk endometrial glandular hyperplasia (E.H.) conditions from the hysteroscopic and hysterologic points of view.

The first study on the administration of LH-RH Analogue to symptomatic patients was conducted by Shaw & Fraser in 1984 ([9]).

LH-RH analogue is a group of drugs which, if administered continuously, cause desensibilization, thus producing a loss of responsiveness to LH-RH (down-regulation) and consequent suppression of target organ gonadotropin incretion. The resulting endocrinal activity suppresses the hypophysiovulvar stimulus resulting in temporary hypogonadism with consequent endometrial atrophy ([10, 11, 12]).

LH-RH analogues are not active when taken orally because they are inactivated by gastric enzymes. For this reason they are administered by nasal aerosol, by subcutaneous injection, or by implanting slow-releasing microspheres and intramuscular injection ([13]).

This constant, slow-release is certainly the most effective means of obtaining suppression of ovarianstereoidogenesis, this being possible following the formulation depot with a release of 100 μg/die of the active substance.

MATERIALS AND METHODS

Seventy five patients, aged between 40 and 55 years, with hysteroscopic and histological diagnoses of low risk endometrial hyperplasia, with normal functional hormone activity and no acute infection or chronic methabolic disease, were selected and studied over a period starting in January 1990 and ending in June 1992.

Thirty eight patients (50.7%) reported atypical uterine bleeding from 1 up to 12 months: 15 patients (20%) in perimenopausal age reported relapsing metrorrhagic cycles, 18 showed doubtful ultrasonography results (increase of endometrial pattern) and 4 were under treatment with Tamoxifen (Nolvadex) (tab. 1).

Table 1. – *Hysteroscopy indications.*

Indications	N.	%
Abnormal uterine bleeding	38	50.7
Relapsing metrorrhagia	15	20
Suspect ultrasounds	18	2.4
Risk factors	4	5.3

The criteria for inclusion were as follows:

— over 40 years of age;

— hysteroscopic / histological diagnosis of simple glandular, polypoid and microcystic glandular endometrial hyperplasia (low-risk endometrial lesions);

— an FSH lower than 30 mIU/ml;

— no presence of acute infection or chronic metabolic disease;

— no history of hormonal therapy in the previous six months.

All patients were treated by intramuscular slow-release LH-RH Analogue, every 28 days for 4 cycles.

Before starting the treatment, patients were administered a dose of gonadotropic and sexual hormone serum with monthly boosters throughout the period of therapy. KIT RIA determines LH and FSH serum levels within a 1.5-200 ml range. Estradiol KIT RIA determines the amount of E_2 with a standard 25 to 2000 pg/ml curb directly.

The statistical analysis of laboratory data was carried out by taking into account the variation of repeated measures. All the data were expressed as mean ± SEM.

Menstrual blood loss was measured by the alkaline haematic method [14]. The number of pads were counted and the length of period in days was recorded. At each visit the women were asked about the number of days they considered their loss to be heavy or light. Target biopsy was performed at the beginning and end of treatment and again three to six months later. Further screening was carried out one year after the end of treatment. The instrument used was the Hamou microcolpohysteroscope, 25 cm long, 4 mm diameter, 90°-wide angle field, oblique-hole vision of 30°, which provides both panoramic and contact view, changing the enlargements during the same investigation.

The optical system is cased in a 5 mm Ø sheath which allows the passage of CO_2 used for distending the uterine cavity. Lighting is provided by a 250 watt light source connected to the device by a flexible optical fibre cable [15]. These characteristics allow hysteroscopic examination at ambulatory level with good patients' acceptability [16, 17, 18]. The hysteroscopic diagnosis of low-risk endometrial hyperplasia was based on the following primary morphological criteria. We were able to draw up such criteria both for low-risk endometrial hyperplasia, as follows:

— exuberant development of endometrial mucosa;

— increased and uneven thickness;

— thickening of glandular orifices;

— increased vascularization;

— presence of cystic dilatations;

— diffused polypoid aspects.

And for the medical treatment effectiveness, as well as its consequent macroscopic modifications of endometrial mucous:

— normally functional endometrium.

After menstruation and up to the tenth day of the cycle the endometrium is pale in colour with a smooth surface with a thickness optically measured of 3-4 mm. The glands can be easily distinguished even though they display no protrusions.

From the eleventh to the thirteenth day of the cycle the endometrium is more congested, red in colour and smooth with a thickness of 5-6 mm, with more easily distinguished glandular orifices.

In the ovulation phase the endometrium tends to become pale, with a thickness of approx. 7-8 mm, and with a bright fleshy appearance due to edema of the stroma. The mucous is denser in aspect and the glands are slightly exposed, corresponding to the presence of secreted serum in the uterine cavity.

In the secretion phase the edematous appearance is lost along with the intracavitary serum.

The endometrium takes on a yellowish, velvety appearance. Occasionally the glands seem pseudocystic. There is a more marked vascularization, which takes the form of spirals around the glandular orifices.

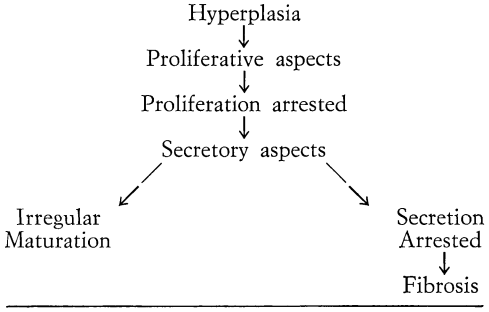
These modifications are most pronounced before menstruation.

Atrophic endometrium. The endometrium undergoes a distinct involution and becomes extremely pale, even clear white in advanced atrophy. Glandular orifices are few in number and scarcely visible. Small haemorrhagic suffusions (petechia) can be observed [19].

Histology provided the following pattern:

— an increase in the number of tissular elements, both epithelial and stromal;

Table 2. – *Histological modifications in response to treatment.*



— abundant desquamation of wide strips of mucosa;

— abnormal increase in stromal cells;

— increased size of all nuclei with normal chromatinic distribution and nucleoli;

— normal pseudostratification and insignificant mitotic activity;

—a « gruyere-like appearance » of the endometrial glands which appear very uneven, representing the most typical diagnostic picture [20].

The effectiveness of treatment evaluated histeroscopically was confirmed from the anatomopathological point of view, according to the scheme proposed by Dallenbach-Helleweg and Ludwig [21] (tab. 2).

Arrested proliferation characterizes a morphological situation where there is a reduction in the number of mitosis of the glandular epithelia, a disappearance of the tortuosity of the glands and pseudostratification of the stroma.

In the *Arrested secretion*, stromal pseudodecidualization and glandular atrophy were noted.

Fibrosis is characterized by small, atrophic glands, and a dense, fibrotic stroma. The maximal response of the endometrium to LH-RH A is the presence of fibrosis and arrested secretion.

Irregular Maturation is characterized by the simultaneous presence of proliferative and secretory glands contained in an edematous and slack stroma.

RESULTS

The behaviour of blood loss evaluated during and after therapy was the first result of treatment with LH-RH analogues to be found in 75 patients presenting low-risk endometrial hyperplasia (tab. 3).

The appearance of amenorrhea occurred within the first 4 weeks of treatment in 66.7% of the patients, and within 16 weeks in 96% in them.

In the follow up at 3 months, a normalisation of the menstrual cycle was observed in 40% of cases, and persistance of amenorrhea in 40 patients, equivalent to 53.3%; 6 months after treatment 25 patients, i.e. 33.3%, reported a persistent amenorrhea, 4 of whom were aged between 40 and 47 years. Three patients reported spotting and 12 hypoamenorrhea, all of them were aged between 49 and 53 years.

In 35 patients in perimenopausal age, menstrual cycle normalised after an average interval of 85 days (range 67-106).

In all patients, ovulation was inhibited and Progesterone serum levels never exceeded 1.0 nanograms during the whole therapy. LH FSH serum levels ranged from 16.2 ± 1.6 to 25.4 ± 1.8, whereas FSH serum levels ranged from 8.9 ± 1.2 to 4.8 ± 1.0. For the latter, the first

Table 3. — *Trend of bleeding in study group.*

Flow	Pre-therapy	1 month therapy	4 months therapy	Follow-up at 3 months after the end of treatment	Follow-up at 6 months after the end of treatment	Follow-up at 1 year after the end of treatment *
Heavy	26 (80%)	—	—	—	—	2 (13.4%)
Normal	—	—	—	30 (40%)	35 (46.7%)	5 (33.3%)
Hypoamenorrhea	—	10 (13.3%)	3 (4%)	—	12 (16%)	3 (20%)
Spotting	11 (14.7%)	15 (20%)	—	5 (6.7%)	3 (4%)	—
Amenorrhea	4 (5.3%)	50 (66.7%)	75 (96%)	40 (53.3%)	25 (33.3%)	5 (33.3%)

* One year after the end of pharmacologic treatment, follow-up only concerns 15 patients out of the 75 of the study group.

Table 4. — LH, FSH and E_2 serum concentration in 75 patients with endometrial hyperplasia low-risk before, during and after treatment with LH-RH analogue.

Month	FSH (mIU/ml)	LH (mIU/ml)	E_2 (pg/ml)
Pre-treatment	10,2±1,5	18,3±1,8	141,0±37
1	4,8±1,0	25,4±1,8	29,6± 4,2
2	6,8±1,8	24,1±1,6	23,7± 3,1
3	7,4±1,0	19,6±1,4	<20
4	8,9±1,2	16,2±1,6	<20

check-up only showed significant suppression, with insignificant differential values rising to 8.9± 1.2 during the 4th month of treatment.

Four weeks after the beginning of the treatment, gonadal suppression was deep and uniform in all patients. Estradiol (E_2) values were equal to 29.6 ± 4.2. Starting from the 2nd month up to the fourth, post-menopausal values were observed (tab. 4).

The level of Prolactinaemia showed no change, whereas total Testosterone dipped significantly from the second month to the end of treatment.

The histological evaluation of the effectiveness of treatment is summarised in (tab. 5).

Analysis of data showed that endometrial hyperplasia was still present in three cases, 4 months after treatment (4%). This result however cannot be interpreted as a failure of the pharmacological treatment, because symptomatology improved (from metrorrhagia to hypoamenorrhea) and the hysteroscopic picture showed a reduction of the exuberant areas with normalisation of the vascularization.

Thirty four patients (45.3%) showed better response to therapy, with arrested proliferation (16%), arrested secretion (18.6%), proliferative aspects (6.6%), and secretory aspects (4%) (tab. 6). Furthermore, in all the cases where the sampling was poor for the histological diagnosis, the hysteroscopic investigation confirmed situations of hypoatrophy and atrophy (40%). The cases of histologic diagnosis of proliferative (6.6%) and secretive endometrium (4%) represent a partial endometrial response to the pharmacological treatment; even though a regression in the hyperplasic aspect is hysteroscopically evident (tab. 7).

This evaluation was repeated for all the patients six months after the suspension of the pharmacological treatment and for 15 patients only at one year (tab. 8). At the six months' follow up, only 2 patients, equivalent to 2.7% of cases, had a histologic diagnosis of simple glandular hyperplasia, while hysteroscopy showed a functional endometrium. From a clinical point of view these patients reported normal menstrual flow. In

Table 5. — *Hystologic diagnosis in 75 women treated with LH-RH A.*

	After 4 months of therapy		Follow-up at 6 months from the end of treatment		Follow-up at 1 year from the end of treatment in 15 women	
	N. pts	%	N. pts	%	N. pts	%
Low-risk hyperplasia	3	4	2	2.7	–	–
Proliferative aspects	5	6.6	30	40	4	26.7
Arrested proliferation	12	16	3	4	3	20
Secretive aspects	3	4	15	20	3	20
Arrested asecretion	14	18.7	3	4	1	6.7
Fibrosis	8	10.7	12	16	2	13.3
Poor sample	30	40	10	13.3	2	13.3

Table 6. — Hysteroscopic vs histologic diagnosis in 75 women treated with LH-RH A after four *months of theraphy.*

Hysteroscopy	HISTOLOGY							
	Low risk hyperplasia %	Proliferative aspects %	Arrested proliferation %	Secretory aspects %	Arrested segretion %	Fibrosis %	Poor sample %	Total
Low risk hyperplasia	–	–	—	–	—	–	—	—
Proliferative endometrium	3 (4)	2 (2.6)	3 (4)	–	—	–	—	8
Secretory endometrium	–	1 (1.4)	5 (6.6)	3 (4)	4 (5.3)	–	—	13
Hypoatrophy atrophy endometrium	–	2 (2.6)	4 (5.4)	–	10 (13.4)	8 (10.7)	30 (40)	54
Total	3 (4)	5 (6.6)	12 (16)	3 (4)	14 (18.7)	8 (10.7)	30 (40)	54

Table 7. — *Hysteroscopic vs histologic diagnosis in 75 women treated with LH-RH A follow-up at 6 months from the end of treatment.*

Hysteroscopy	HISTOLOGY							
	Low risk hyperplasia %	Proliferative aspects %	Arrested proliferation %	Secretory aspects %	Arrested secretion %	Fibrosis %	Poor sample %	Total
Low risk hyperplasia	–	—	–	—	–	—	—	—
Proliferative endometrium	2 (2.7)	25 (33.3)	–	8 (10.7)	–	—	—	35
Secretory endometrium	–	5 (6.7)	–	7 (9.3)	–	—	—	12
Hypoatrophy atrophy endometrium	–	—	3 (4)	—	3 (4)	12 (16)	10 (13.3)	28
Total	2 (2.7)	30 (40)	3 (4)	15 (20)	3 (4)	12 (16)	10 (13.3)	

Table 8. — *Hysteroscopic vs histologic diagnosis in 15 women treated with LH-RH A follow-up at 1 year from the end of treatment.*

Hysteroscopy	HISTOLOGY							
	Low risk hyperplasia %	Proliferative aspects %	Arrested proliferation %	Secretory aspects %	Arrested secretion %	Fibrosis %	Poor sample %	Total
Low risk hyperplasia	–	–	–	–	–	–	–	–
Proliferative endometrium	–	2 (13.4)	–	–	–	–	–	2 (13.3)
Secretory endometrium	–	2 (13.3)	–	3 (20)	–	–	–	5 (33.3)
Hypoatrophy atrophy endometrium	–	–	3 (20)	–	1 (6.7)	2 (13.3)	2 (13.3)	8 (53.3)
Total	–	4 (26.7)	3 (20)	3 (20)	1 (6.7)	2 (13.3)	2 (13.3)	

Table 9. — *Hysteroscopy vs histology.*

	Hysteroscopy N. (%)	Histology (N. (%)
Low risk hyperplasia	67 (89.3)	75 (100)
Proliferative endometrium	6 (8)	—
Secretory endometrium	2 (2.7)	—

33.3% of the cases a situation of endometrial atrophy was visualised hysteroscopically: in 20% of such cases it corresponded to the histologic investigation whereas in 13.3% it was not possible to draw a histologic diagnosis.

Only 15 patients (20% of cases) underwent hysteroscopy one year after treatment. Low-risk endometrial hyperplasia was never confirmed either by hysteroscopy or by histology; in 46.6% of the cases there was a diagnostic correspondance between the two methods in the diagnosis of normal endometrium.

Before treatment the correspondence of diagnosis between hysteroscopy and histology was equivalent to 89.3% (tab. 9).

In order to assess their tolerance degree, patients were classified into four groups on the basis of the intensity of pain caused by the investigation (tab. 10).

The side effects of treatment with LH-RH analogue are connected to the consequent hypoestrogenism; they were however, well tolerated by the patients and did not require suspension of treatment (tab. 11).

CONCLUSIONS

The hysteroscopic and histologic evaluation of the endometrial modifications induced by LH-RH analogue demonstrated the effectiveness of this drug in the treatment of 96% of the cases of low risk endometrial hyperplasia. Only in 4% of the cases was hyperplasia still present in the histologic sampling, 4 months after treatment.

Table 10. — *Degree of tolerance to hysteroscopic investigation.*

Tolerance	Before	After	Follow-up 3 months	Follow-up 6 months
Excellent	40 (53.3%)	35 (46.7%)	37 (49.3%)	43 (57.3%)
Good	20 (26.7%)	22 (29.3%)	25 (33.3%)	20 (26.7%)
Moderate	12 (16%)	13 (17.3%)	11 (14.7%)	10 (13.3%)
Poor	3 (4%)	5 (6.7%)	2 (2.7%)	2 (2.7%)
Total	75 (100%)	75 (100%)	75 (100%)	75 (100%)

Excellent: no inconvenience. Good: minimum inconvenience, which did not affect the test times.

Table 11. — *Side effects of treatment with LH-RH analogue.*

	2 Months of Therapy	4 Months of Therapy	Follow-up after 3 months of treatment	Follow-up after 6 months of treatment
Hot flush	53 (70.7%)	68 (90.7%)	30 (40%)	23 (30.7%)
Headache	10 (13.3%)	7 (9.3%)	2 (2.7%)	—
Change of mood	16 (21.3%)	23 (30.7%)	7 (9.3%)	5 (6.7%)
Depression	10 (13.3%)	14 (18.7%)	5 (6.7%)	3 (4%)
Dizziness	8 (10.7%)	14 (18.7%)	2 (2.7%)	2 (2.7%)
Decrease of libido	27 (36%)	16 (26.7%)	6 (8%)	6 (8%)
Vaginal dryness	30 (40%)	20 (26.6%)	8 (10.7%)	6 (8%)
> weight +1-2 kg	19 (25.3%)	9 (12%)	6 (8%)	3 (4%)

Hysteroscopy is proposed both in the initial diagnosis of endometrial hyperplasia and in post-therapy follow-up.

It is particularly useful in case where it is not possible to perform a satisfactory biopsy (40% of cases), as it provides a more comprehensive view of the endometrial mucosa and represents the only method of diagnostic evaluation stating the absence of truly pathological aspects.

Histology is still necessary for evaluating the persistance or regression of endometrial hyperplasia.

However endoscopic investigation anables target biopsy sampling and it is therefore essential to define the localisation, size and gravity of the endometrial pathology. On accont of the patient's high acceptability and of the absence of complications, this method proves to be simple and with no traumas, thus allowing further application in the future, if required. Such results are extremely important as to endometrial hypoplastic pathology, taking into account the need for on-going, regular check-ups, which allows keeping the albeit limited oncogenous risks under control.

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