The effectiveness of Danazol therapy in postmenopausal women affected by endometrial hyperplasia

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Summary: Forty eight patients in postmenopause affected by histologically confirmed endometrial hyperplasia (34 with simplex and 14 with complex forms) were administered Danazol therapy, 400 mg/day for 3 consecutive months.

At the end of treatment, regression of the endometrial hyperplasia was histologically ascertained in 46 patients (95.9%) with disappearance of the metrorrhagia. Endometrial atrophy was obtained in 75% of the cases, while secretive (14.7%) or proliferative (6.2%) aspects resulted in the others. Only 2 patients (4.1%) showed persistence of the hyperplastic endometrium.

On the basis of this experience, treatment with Danazol appears to be effective and safe with only scarce and transient side effects. This therapy is therefore proposed as a valid alternative to progestogen therapy in cases of postmenopausal endometrial hyperplasia.

Key words: Endometrial hyperplasia; Danazol.

INTRODUCTION

Endometrial hyperplasia is principally related to a hormone condition of absolute or relative hyperestrogenism, as may be observed in cases of chronic anovulation. In post-menopausal women this pathological condition has long been considered at risk for neoplastic transformation because of the abnormal conversion of plasma androstenedione into estrone or to non-balanced substitutive estrogen-therapy ([1, 2]).

The rate of progression to adenocarcinoma in the international literature is controversial ([3, 4, 5, 6, 7]), although it seems to be closely related to the architectural and cytologic structure of the hyperplastic growth itself.

In a prospectic study conducted on 170 patients affected by endometrial hyperplasia and followed for 11 to 15 years, Kurman stated that the progression rate to adenocarcinoma was less than 2% for hyperplasias without cytologically atypia, whereas more than 20% of the atypical hyperplasias progressed to adenocarcinoma ([8]).

Although a significant number of typical hyperplastic lesions will revert spontaneously, a hormonal treatment has usually been advocated ([6]).

The therapeutic approach to hyperplastic endometrium has been widely represented by progestins ([3, 9, 10, 11, 12, 13]) that induce a suppression of endometrial growth

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and therefore produce atrophic changes in 16% ([5]) to 25% ([13]) of the patients, with the consequent disappearance of uterine bleeding.

A synthetic steroid (Danazol), a derivative of 17-alpha-ethinyltestosterone (ethisterone) and commonly used in benign breast diseases ([14, 15]) as well as in endometriosis ([16, 17]), has been proposed as an alternative to progestogen therapy for treating endometrial hyperplasia at a dosage of 200-600 mg/day for 1 to 3 months.

The main biologic property of Danazol is its capacity to cause atrophic endometrial changes, leading to the consequent regression of the hyperplastic lesion ([18, 19, 20]); a "progestin-like" activity ([21, 22]) due to the binding of the steroid to the progestin receptors has also been documented. An inhibition of the steroid sulphatase activity with a consequent reduction of the conversion of estrone to estradiol has also been reported ([23]).

The clinical results obtained with Danazol in endometrial hyperplasia are very encouraging ([24, 25, 26, 27]) and consist of regression of hyperplastic lesions with a high rate of atrophic modification (68% to 100%) and disappearance of the associated menometrorrhagia.

The aim of the study was to evaluate the efficacy of Danazol therapy in post menopausal patients affected by histologically proven endometrial hyperplasia.

MATERIALS AND METHODS

Forty eight postmenopausal women affected by symptomatic endometrial hyperplasia who had received no prior treatment for this pathology, were enrolled in the study.

All the patients were observed in the outpatient clinic of the Division of Gynecologic Oncology of the "Regina Elena" National Cancer Institute of Rome.

The mean age was 55.2 years (range 46-70) and the average interval from the menopause was 5.8 years (range 1-20).

All the patients were submitted to diagnostic endometrial curettage with Novak's curette. According to the classification proposed by the International Society of Gynecological Pathologists, the lesions were divided into: simplex hyperplasias (SH- previously defined as "cystic") in 34 patients (29.2%), and complex hyperplasias (CH- synonymous with "adenomatous") in 14 (70.8%).

Patients affected by atypical hyperplasia were excluded from the protocol and were submitted to hysterectomy in agreement with Norris ([28]) and Ferenczy ([29]).

Other criteria of exclusion giving contraindications to Danazol therapy were: heart or renal failure, diabetes and defects of the coagulation system.

As already described in international literature ([5]), a relationship between age of incidence and histologic type of hyperplasia was observed: 48.2 years for the simplex glandular hyperplasia and 54 for the complex form.

Vaginal bleeding was subjectively classified as mild in 30 patients (62.5%), moderate in 15 (31.2%) and severe in 3 (6.2%).

All the patients received Danazol at a dosage of 400 mg/day for 3 consecutive months, at the end of which the patients were again submitted to endometrial curettage.

In addition, 33 cases of symptom-free patients with hyperplastic endometrium which converted to normal after Danazol therapy were observed 4 months after stopping the treatment, in order to evaluate its long-term effects.

RESULTS

At histopathological examination carried out after 90 days of continuous Danazol treatment (Table 1), 95.9% of the patients (46 out of 48) showed a conversion of the hyperplastic endometrium into normal: 75% had atrophic transformation, while secretory or proliferative changes were observed respectively in 14.6% and 6.2% of the patients.

Therapy was quite well tolerated and no patient had to interrupt, treatment, nor did any patients withdraw from the study.

Side effects, which promptly disappeared after the end of the treatment, were limited to moderate weight-gain in 5 subjects, headache in 4 and gastrointestinal disorders in another 4.

Table 1. – *Efficacy of Danazol therapy in post-menopausal patients with endometrial hyperplasia.*

	No. of patients	Endometrium (%)			
		Atrophic	Secret.	Prolif.	Hyperplastic
SH	34	26 (76.4)	5 (14.7)	2 (5.9)	1 (2.9)
CH	14	10 (71.4)	2 (14.2)	1 (7.1)	1 (7.1)*
Total	48	36 (75.0)	7 (14.6)	3 (6.2)	2 (4.1)

SH = Simplex hyperplasia; CH = Complex hyperplasia; (*) = Atypical cytological features.

Uterine bleeding disappeared in an average time of 26.9 days (range 12-43) from start of treatment.

At histologic control only 2 patients (4.1%) had a persistence of the uterine symptomatology with unchanged hyperplastic endometrium at the histologic control. One of these non-responders, previously affected by complex hyperplasia, showed atypical cytological features after therapy and was than referred to the hospital for hysterectomy. The other patient with persistent hyperplasia remained classified as simplex and was submitted again to Danazol.

Of the 33 patients who were observed four months after ending therapy, 3 (8.1%) reported a recurrence of uterine bleeding due to the hyperplastic growth of the endometrium (Table 2).

In terms of recurrences, no significant differences were observed between the simplex and the complex hyperplastic lesions: 8% vs 12.5%.

All the hyperplastic recurrences were classified as simplex and Danazol therapy was then resumed at the same dosage for another 3 months.

CONCLUSION

The prognostic significance of endometrial hyperplasia must still be accurately established. Some authors previously reported that hyperplastic lesions (mainly those described as adenomatous) may represent a precancerous condition ([3, 4]).

In a retrospective review, Sherman *et al.* ([7]) reported that 72% of patients affected by endometrial adenocarcinoma had had a previous diagnosis of adenomatous or atypical adenomatous hyperplasia.

Others prospectively examined the behavior of the variety of hyperplastic forms and stated that the risk of neoplastic transformation is low ([6, 8]). Furthermore Gambrell pointed out that "... any degree of endometrial hyperplasia may be a significant lesion for postmenopausal women" ([5]).

Since hyperplasia displaying evidence of cyto-architectural atypical aspects seems to be at risk for neoplastic progression, the elective management is hysterectomy in postmenopausal women.

On the contrary, simplex or complex hyperplasias without atypia are usually treated with hormone therapy during the fertile age as well as in menopause.

Progestinic treatment, widely used in cases of hyperplastic endometrium, has provided good results ([5, 10, 11, 12, 13]), although inadequate clinico-pathological responses have been documented. Persistent

Table 2. – *Follow-up at 4 months from suspension of Danazol therapy.*

	No. of patients	Recurrence (%)
SH	25	2 (8.0) *
CH	8	1 (12.5) *
Total	33	3 (9.1)

(*) Simplex hyperplasias.

Table 3. – *Efficacy of Danazol treatment in endometrial hyperplasia.*

Author	(Ref.)	Patients	Dosage	Regression (%)	Atrophy (%)
Jasonni	(26)	10 *	600 mg/day × 1 mo	100	70
Bulletti	(24)	31 *	400 mg/day × 3 mos	92	68
Busacca	(30)	10 **	200 mg/day × 3 mos	100	10
Terakawa	(27)	5 ***	400 mg/day × 3 mos	100	100
Soh	(25)	15 ***	400 mg/day × 3 mos	100	100

* = Postmenopause; ** = Premenopause; *** = Pre- and postmenopause; Ref = Reference.

hyperplasia is reported at a rate ranging from 5.5% ([5]) to 7% ([13]).

Danazol, a synthetic steroid derivative of ethisterone usually employed in endometriosis and benign breast diseases, has provided excellent results for treating hyperplastic endometrial lesions.

The antiestrogenic property of Danazol, the "progestin-like" activity and the effect on the hypothalamic pituitary functions lead to a suppression of endometrial growth. This is probably also due to a decrease of estrogen receptors (ER) and to a disappearance of EFG-R previously frequently detected in the hyperplastic endometrium ([31]).

The results reported in the international literature (Table 3) point to the efficacy of Danazol at a dosage of 200-600 mg/day for 1-3 months. Endometrial atrophic transformation with therapy at 400 mg/day for 90 days ranged between 68% ([24]) and 100% ([25, 27]).

In the present experience, the overall response in terms of atrophic changes was 75%. This result was not significantly related to the type of hyperplasia: 76.4% for the simplex and 71.4% for complex lesion. The figures are comparable to those reported by Soh and Sato in 1990 using the same therapeutic approach ([25]).

In a large series treated with progestogen therapy Gambrell ([5]) showed a similar rate of hyperplasia reverting to normal (94.5%), but only 16% displayed atrophic changes.

The overall 95.9% conversion rate of hyperplastic endometrium into normal (with secretory or proliferative modifications) or atrophic that we observed is in accord with that reported in the literature.

The overall rate of failure was limited to only 4%, with no significant differences between simplex (2.9%) or complex (7.1%) hyperplasia.

Four months after interrupting therapy, 9.1% of the patients showed a recurrence of the endometrial hyperplasia followed by uterine bleeding. In literature a 20% rate of recurrence is documented at 3 months from the cessation of therapy ([25]), while Terakawa reports all patients as symptom-free within a 9-month of follow-up period ([27]).

The other 30 cases (90.9%) observed during the follow-up of the present study were, symptom-free and showed no signs of endometrial growth.

Therapy with Danazol, as previously documented, has been generally well tolerated with only mild and transitory side effects. This treatment therefore seems to be highly effective in inducing a stable regression of endometrial hyperplasia in postmenopausal women (regardless of the histological type of hyperplasia) and, although further clinical studies must confirm the efficacy of Danazol, its role is promising as an alternative to progesterone therapy.

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