Regression of endometrial hyperplasia after treatment with the gonadotrophin-releasing hormone analogue triptorelin: a prospective study

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Endometrial hyperplasia is thought to be caused by the prolonged, unopposed oestrogenic stimulation of the endometrium. The regression of hyperplastic back to normal endometrium is the main purpose of any conservative treatment in order to prevent development of adenocarcinoma. The aim of this study was to evaluate the regression of hyperplastic to normal endometrium in patients with various forms of endometrial hyperplasia after treatment with the gonadotrophin-releasing hormone analogue (GnRHa) triptorelin for 6 months. Fifty-six patients with endometrial hyperplasia were enrolled in this trial; 39 patients (group I) presented simple hyperplasia, 14 (group II) complex hyperplasia and three (group III) atypical hyperplasia. All patients were treated with triptorelin for 6 months. Bleeding control during treatment was excellent. A post-treatment curettage for estimation of changes of the glands and the stroma, ranging between the normal proliferative endometrium and the well-differentiated adenocarcinoma (Silverberg and Kurman, 1992). These proliferative disorders of the endometrium are thought to be caused by the prolonged unopposed oestrogenic stimulation of the endometrium either endogenously or exogenously. According to the classification of the International Society of Gynecological Pathologists (ISGP) and the World Health Organization (WHO), based largely on the previous work of Kurman and Norris (Kurman and Norris, 1982; Kurman et al., 1985), the architectural and cytological features of the endometrium are evaluated independently; the architecture is classified as simple or complex and the cytological features as normal or atypical.

Thus, the endometrial hyperplasias are classified as (i) simple (formerly called glandular and/or glandular–cystic), (ii) complex (formerly called adenomatous), (iii) simple with atypia and (iv) complex with atypia (formerly called adenomatous with atypia) (Silverberg and Kurman, 1992).

Endometrial hyperplasias have been treated either conservatively or surgically depending on the histopathological form, the age of the patient and the presence of other risk factors (Gal et al., 1983; Wentz, 1985). The main purpose of both types of therapy is prevention of endometrial cancer development, although sometimes bleeding control is of crucial importance. The disadvantage of the surgical methods (hysterectomy, hysteroscopic endometrial resection/ablation) is that they are based on the removal or disruption of the endometrium. On the other hand, the aim of the conservative treatment is the regression of the hyperplastic to normal endometrium.

Conservative treatment of endometrial hyperplasia is based on the administration of agents with either anti-oestrogenic action or direct anti-proliferative effect on the endometrium. Progestagens have been used widely in the treatment of endometrial hyperplasias, especially of the simple forms, with satisfactory results (Wentz, 1974, 1985; Gal et al., 1983; Kurman et al., 1985; Ferenczy and Gelfand, 1986, 1989; Gal 1986; Affinito et al., 1994). The administration of clomiphene citrate was also reported (Wall et al., 1965; Chamlian and Taylor, 1970; Kurman et al., 1985), but the data are extremely limited and the results seem to be very poor. More recently, danazol has also been administered for the treatment of endometrial hyperplasia with satisfactory results (Jasonni et al., 1986; Bullett1 et al., 1987; Busacca et al., 1987; Terakawa et al., 1988; Soh and Sato, 1990; Sedati et al., 1992).

Another option in the conservative treatment of endometrial
Endometrial hyperplasia could be the use of gonadotrophin-releasing hormone agonists (GnRHa). GnRHa are a group of synthetic compounds which are derived from natural GnRH through substitution of amino acids at position 6 and/or 10. Their functions by down-regulating the GnRH receptors and inhibiting the post-receptor mechanisms. Moreover, recent data support a direct antiproliferative effect of GnRHa on the endometrium (Emons et al., 1993). Furthermore, GnRHa were used in the management of patients with recurrent endometrial carcinoma resistant to other treatment modalities, with promising results (Gallagher et al., 1991; De Vriese and Bonte, 1993). The aim of this study was to evaluate the regression of hyperplastic to normal endometrium in patients with various forms of endometrial hyperplasia after treatment with the GnRHa triptorelin for 6 months.

Materials and methods

Patients

In all, 56 patients with hyperplasia of the endometrium were studied prospectively between October 1992 and June 1996. The patients’ mean age was 46.2 ± 5.6 years (range 30–54 years). All patients presented with abnormal vaginal bleeding and the diagnosis of the disease was based on the histological examination of the endometrial samples obtained by curettage. The clinical characteristics of the patients are shown in Table I. In 36 (64.3%) cases, the patients had had a previous history of abnormal vaginal bleeding, in 20 (35.7%), there had been a previous curettage for that bleeding and in seven (12.5%) cases, the endometrial sampling had been positive for endometrial simple (adenocystic) hyperplasia (Table I). Obesity was present in 22 (39.2%) patients.

Endometrial hyperplasias were classified according to the IGPG/WHO system. A re-evaluation of the endometrial pathology was done by the same pathologist. The pathologist was blind to the original data in order to have a more objective and uniform classification of endometrial histology. This was done since in some cases of endometrial hyperplasia with borderline architectural and cytological characteristics, differential diagnosis among the different types is not easy and may differ from one observer to another (Silverberg and Kurman, 1992). Thus, potential biases may arise from a failure to blind the pathologist to the original data. Biases may also result from curettage itself since, sometimes, areas of the endometrium may not be sampled adequately, leading to underestimation of endometrial pathology (Silverberg and Kurman, 1992).

The patients were divided into three groups, according to the type of endometrial hyperplasia: group I consisted of 39 patients with simple (adenocystic) hyperplasia, group II consisted of 14 patients with complex (adenomatous) hyperplasia and group III consisted of three patients with atypical complex (atypical adenomatous) hyperplasia. Patients with different forms of endometrial hyperplasia present were classified according to the most serious histological pattern. Thus, in nine out of 14 cases with complex hyperplasia there were areas with simple hyperplasia, and in all cases of atypical complex there were areas with complex hyperplasia as well. The clinical characteristics of the patients in the different groups are shown in Table I.

Treatment

In order for a patient to enter the study, she had to fulfil the following criteria: (i) premenopausal, (ii) negative clinical and ultrasound examination for the presence of adnexal diseases and (iii) negative history for osteoporosis. The study was approved by the Aristotelian University of Thessaloniki and by the Scientific Committee of the Hippokration General Hospital. Informed consent was also obtained from all patients before treatment.

The GnRHa triptorelin (Arvekap 3.75 mg; Ipsen, PharmaBiotech, Paris, France) was administered every 4 weeks for a period of 6 months by i.m. injection of 3.75 mg in the form of sustained-release microcapsules. The first injection was given, usually, on the first or the second day of the cycle. In cases with amenorrhea lasting >2 months, due to the pre-climacteric status of the patient, the treatment was started independently of the menstrual period.

Table I. Clinical characteristics of the patients

<table>
<thead>
<tr>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>simple hyperplasia</td>
<td>complex hyperplasia</td>
<td>atypical hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Patients (n)</td>
<td>39</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Age (mean ± SD, years)</td>
<td>46.2 ± 5.9</td>
<td>46.0 ± 5.5</td>
<td>47.0 ± 1.0</td>
</tr>
<tr>
<td>Duration of bleeding (mean ± SD, days)</td>
<td>14.5 ± 12.2</td>
<td>21.3 ± 15.2</td>
<td>15.0 ± 7.0</td>
</tr>
<tr>
<td>History of bleeding (n)</td>
<td>24 (61.5)</td>
<td>10 (71.4)</td>
<td>2 (66.6)</td>
</tr>
<tr>
<td>Duration (mean ± SD, months)</td>
<td>30.2 ± 28.1</td>
<td>23.4 ± 22.3</td>
<td>9.0 ± 4.2</td>
</tr>
<tr>
<td>Previous curettage (n)</td>
<td>13 (33.3)</td>
<td>6 (42.8)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Normal endometrium (n)</td>
<td>8 (20.5)</td>
<td>4 (28.5)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Endometrial hyperplasia (n)</td>
<td>5 (12.8)</td>
<td>2 (14.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Adenomatous (simple) (n)</td>
<td>5 (12.8)</td>
<td>2 (14.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Adenomatous (complex) (n)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Family history of cancer</td>
<td>9 (23.0)</td>
<td>4 (28.5)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Gynaecological (n)</td>
<td>4 (10.2)</td>
<td>1 (7.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Pregnancies</td>
<td>2.2 ± 1.3</td>
<td>2.4 ± 1.0</td>
<td>2.0 ± 0.0</td>
</tr>
<tr>
<td>Labours (n)</td>
<td>1.4 ± 1.6</td>
<td>0.7 ± 0.9</td>
<td>1.3 ± 1.1</td>
</tr>
<tr>
<td>Abortions (n)</td>
<td>3 (7.7)</td>
<td>1 (7.1)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Diabetes mellitus (n)</td>
<td>3 (7.7)</td>
<td>4 (28.5)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>15 (35.7)</td>
<td>5 (35.7)</td>
<td>2 (66.6)</td>
</tr>
<tr>
<td>Obesity (n)</td>
<td>2 (5.1)</td>
<td>2 (14.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>PCOS (n)</td>
<td>2 (5.1)</td>
<td>2 (14.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Infertility (n)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.
Regression of endometrial hyperplasia with triptorelin

Table II. Treatment characteristics. Values are means ± SD

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>simple</td>
<td>complex</td>
<td>atypical</td>
<td></td>
</tr>
<tr>
<td>Bleeding duration after the first GnRHa injection (days)</td>
<td>6.2 ± 4.7</td>
<td>6.8 ± 2.5</td>
<td>8.3 ± 1.5</td>
<td>6.4 ± 4.1</td>
</tr>
<tr>
<td>Interval between the first post-treatment menses and the last GnRHa injection (days)</td>
<td>80.8 ± 18.9</td>
<td>84.5 ± 18.2</td>
<td>73.0 ± 7.1</td>
<td>81.2 ± 18.1</td>
</tr>
<tr>
<td>Interval between post-treatment curettage and the last GnRHa injection (days)</td>
<td>101.0 ± 44.7</td>
<td>101.1 ± 30.4</td>
<td>83.9 ± 27.2</td>
<td>100.1 ± 40.0</td>
</tr>
</tbody>
</table>

Clinical and pathologic evaluation

During treatment, the patients were evaluated every 4 weeks (injection days) or earlier for bleeding control and the presence of side-effects. After completion of the treatment and restoration of the pituitary function, a histopathological re-examination of the endometrium was done. Thus, a curettage was usually performed after the first post-treatment menstrual period, which is a clinical sign of pituitary–ovarian axis function restoration. In patients with amenorrhoea lasting >4 months after the last GnRHa injection, the curettage was performed when normal pituitary function was noticed in hormonal post-treatment evaluation [increased follicle stimulating hormone (FSH) and luteinizing hormone (LH)].

The estimation of post-treatment endometrial samples was also done by the same pathologist. Endometrial findings were classified as normal or hyperplastic. Normal endometrium was sub-divided into functional (proliferative, secretory) or atrophic. Endometrial hyperplasias were classified according to the previously mentioned ISGP/WHO system.

Results

The first GnRHa injection was followed by vaginal bleeding of 6.4 ± 4.1 (range 2–25) days and, thereafter, by amenorrhoea during the treatment (Table II). After treatment, 11 patients became menopausal. In the rest, the mean time between the last GnRHa injection and the first post-treatment menses was 81.2 ± 18.1 (range 53–125) days (Table II). Treatment characteristics of the patients in the different groups were similar (Table II).

The endometrium was re-examined histologically in 54 (96.4%) out of 56 patients. One woman, 49 years old, with simple hyperplasia decided to discontinue the treatment and to undergo hysterectomy because of the fear of adenocarcinoma development. Another patient, 42 years old, with simple hyperplasia and an 8 year history of irregular bleeding, refused histological re-evaluation since she was satisfied with the excellent bleeding control following the treatment. The mean time between last GnRHa injection and the post-treatment curettage was 101.1 ± 40.0 days (Table II).

In group I, 37 out of 39 patients were re-evaluated histologically. In 32 (86.5%) of them the endometrium was normal, functional in 21 (56.7%) cases and atrophic in 11 (29.8%) cases (Table III). In five (13.5%) patients, histopathological examination of the endometrium again showed simple hyperplasia (Table III). Three of these patients were obese, one was obese with a history of diabetes mellitus and one was a young woman with polycystic ovarian syndrome (PCOS). The last patient received clomiphene citrate for 6 months after triptorelin treatment and a new endometrial sample was then normal.

Five patients in this group had had a previous history of simple hyperplasia (Table I); post-treatment endometrial pathology was normal in four, while it was positive for simple hyperplasia in the fifth, an extremely obese woman.

In group II, all patients were re-examined histologically. In 12 (85.7%) of them the endometrium was normal, functional in eight (57.1%) and atrophic in four (28.6%) cases (Table III). In two (14.2%) patients, endometrial pathology revealed hyperplasia; in one patient it was again complex hyperplasia, while in the other complex with atypia (Table III). These two patients had had a history of ovulatory disturbances (PCOS). Two patients from this group had had a previous history of simple hyperplasia (Table I); both of them had normal post-treatment endometrial pathology.

In group III, all patients were re-evaluated histologically. None of them had normal post-treatment endometrial pathology. In two cases complex hyperplasia was found and the third complex hyperplasia with atypia was present (Table III). The last was an obese, hypertensive woman with diabetes mellitus.

In some cases, post-treatment endometrium was found in the proliferative or secretory phase of the cycle but with incomplete maturation, probably due to treatment with GnRHa (Table III). During treatment, hot flushes were reported by 38 (67.8%) out of 56 patients and this was the most common side-effect; vaginal atrophy was present in 21 (37.5%) patients, psychological changes in 17 (30.4%) cases, decreased libido in 12 (21.5%) and headaches in seven (12.5%) patients. However, no patient discontinued the treatment because of these side-effects, since they were considered well tolerated.
Discussion

Oestrogens seem to play a key role in endometrial physiology and pathophysiology. Their main physiological action is to induce regeneration and proliferation of the endometrium in order to restore the tissue lost during menstruation. However, this action is held in check mainly by progesterone which causes secretory differentiation of the endometrial tissue. Persistent stimulation by unopposed oestrogen over many years or even decades may lead to endometrial hyperplasia. The histological type of the hyperplasia is linked to the intensity and the duration of the oestrogenic effect (Dallenbach-Hellweg, 1987). Furthermore, prolonging the oestrogenic action on the hyperplastic endometrium may lead to the development of adenocarcinoma, due to the unremitting proliferation of the endometrium. Thus, endometrial hyperplasia is generally considered as a precancerous lesion.

It seems that there are two categories of endometrial adenocarcinomas depending on their origin. The first type are those with endometrial differentiation, which are the more common forms. They are hormone dependent and they seem to develop by way of hyperplasias. The second type are those with Mullerian differentiation (clear cell, papillary, anaplastic), which seem to develop from focal ectopic metaplasia (Dallenbach-Hellweg, 1987). However, the probability of progression from endometrial hyperplasia to well-differentiated adenocarcinoma depends on the severity of the histopathological changes of the hyperplastic endometrium. Hence, there is a gradual increase from the simple to the complex forms especially in the atypical ones.

Thus, treatment of endometrial hyperplasia, apart from the importance of bleeding control in some cases, is important for the prevention of adenocarcinoma development. In addition regression of hyperplastic to normal endometrium is the main purpose of any conservative treatment. This is based on the administration of drugs with either anti-oestrogenic action or direct anti-proliferative effect on the endometrium. Histological monitoring is extremely important in cases of conservative management of endometrial hyperplasia. Progestagens are used widely in the treatment of endometrial hyperplasias. They have an indirect anti-oestrogenic effect, through the decrease of endometrial oestrogen receptors and the increase in conversion of 17-β-oestradiol into the less potent oestrone (Gal, 1986; Casper and Chapdelaine, 1993) as well as a direct anti-proliferative effect on the endometrium (Marshburn et al., 1992; Gnatuk and Ory, 1993).

Several progestagens in various forms and protocols have been used in the treatment of endometrial hyperplasias. Ferenczy and Gelfand (1986, 1989) proposed the use of medroxyprogesterone acetate 10 mg daily cyclically during 11–14 days for 3–6 months in cases of hyperplasias without atypia and 10 mg daily continuously for 3 months and cyclically thereafter in cases of hyperplasias with atypia. Regression to normal endometrium was noticed in 56 (86%) out of 65 patients with simple and/or complex hyperplasia without atypia. Recurrence of the disease was observed in nine (10.7%) cases, but none developed carcinoma. On the other hand, 10 (50%) out of 20 cases with atypical hyperplasia experienced persistence of the disease and five (25%) had recurrence after the discontinuation of the continuous medroxyprogesterone acetate administration. Five (25%) of them developed adenocarcinoma. Persistence of hyperplasia, despite therapy, was the main prognostic factor (four out of five patients) and obesity the main risk factor. Similar findings were reported by Kurman et al. (1985), with a regression rate of 77% for simple or complex hyperplasia without atypia and only 50% in cases with atypia. On the other hand, 30% of the cases with atypia progressed to adenocarcinoma.

Megestrol acetate has been also used for the treatment of endometrial hyperplasia, in daily doses of 20–40 mg continuously (Gal et al., 1983; Gal, 1986) or in daily doses of 80–160 mg for 6–8 weeks (Wentz, 1985). Regression rate was ~90% irrespective of the presence of atypia (Gal et al., 1983; Wentz, 1985; Gal, 1986) and continuous administration seemed to be necessary for recurrence prevention (Eichner and Abella, 1971; Gal et al., 1983; Gal, 1986). The use of levonorgestrel releasing intrauterine devices was also proposed in the treatment of hyperplastic lesions of the endometrium with high regression rates (Volpe et al., 1982; Perino et al., 1987; Scarselli et al., 1988). More recently, Affinito et al. (1994) proposed the use of a vaginal cream containing natural micronized progesterone in patients with simple or complex hyperplasia for a period of 3 months. Regression was observed in 67 (90.5%) out of 74 patients, with better results in cases of simple hyperplasia.

The application of GnRHa for endometrial diseases was initially reported for the management of patients with recurrent endometrial carcinoma, resistant to other treatment modalities, with a regression rate as high as 35% (Gallagher et al., 1991; De Vriese and Bonte, 1993). Treatment of endometrial hyperplasia with GnRHa was theoretically proposed by Kullander (1992) as an alternative to surgical therapy. In our study, the administration of the GnRHa triptorelin for 6 months in patients with simple and/or complex hyperplasia without atypia was followed by a regression rate of ~85% and excellent bleeding control during treatment. The therapeutic application of GnRHa for patients with simple or complex hyperplasia by other investigators was also associated with high regression rates (Menozzi et al., 1992; Garosso et al., 1993; Pozzi et al., 1993; Zagni et al., 1993; Lopez 1994; Vitale et al., 1994; Bonfirraro et al., 1995; Agorastos et al., 1996). Thus, the treatment of non-atypical forms of endometrial hyperplasia with GnRHa for 6 months is associated with regression rates comparable to the administration of progestagens.

The regression of endometrial hyperplasia to normal endometrium is probably due to the following mechanisms: (i) decreased gonadotrophin levels as a result of pituitary downregulation during GnRHa administration. Luteinizing hormone receptors were found in normal endometrium and in human endometrial carcinomas (Reshef et al., 1990; Lei et al., 1992; Lin et al., 1994). It is possible, therefore, that LH could have a direct proliferative effect on human endometrium, which is inhibited during GnRHa administration; (ii) the decreased ovarian steroidogenesis following low gonadotrophin levels (De Leo et al., 1997). This is the more likely mechanism, since oestrogens play a key role in the development of...
endometrial hyperplasia (Kullander, 1992; Emoms and Schally, 1994). Suppression of oestradiol production also seems to play a significant role in the treatment of uterine fibroids with GnRHa (Broekmans, 1996; Golan, 1996; De Leo et al., 1997); (iii) A direct action of the GnRHa itself on endometrium. GnRH receptors as well as triptorelin receptors were found in human endometrial cell lines (Emoms et al., 1988, 1993b; Srkalovic et al., 1990). Moreover, the GnRHa triptorelin and the GnRHa SB-75 (cetrorelix) were found to have a direct antiproliferative effect on human endometrial cancer cells in vitro.

However, there were some cases with non-atypical simple or complex hyperplasia where GnRHa treatment failed to regress the disease. The presence of risk factors such as obesity, diabetes mellitus and ovulatory disturbances may contribute to the persistence of endometrial hyperplasia in some of these patients despite triptorelin administration. Nevertheless, in some of them treatment failure may be due to the presence of permanent genetic changes, as a result of the chronic unopposed oestrogenic stimulation of the endometrium, which could no longer be repressed by the inhibition of oestrogen production and action (Dallenbach-Hellweg, 1987; Bai et al., 1994). Thus, disease persistence or, even worse, progression (as observed in a case of complex hyperplasia) despite therapy may be a risk factor for adenocarcinoma development.

On the other hand, the treatment of atypical forms with triptorelin for 6 months was associated with poor results, although the number of the patients was extremely limited for definite conclusions. Poor results were also observed in the treatment of atypical endometrial hyperplasia with medroxyprogesterone acetate (Ferency and Gelfand, 1986). The presence of atypia in hyperplastic endometrium was found to be positively associated with the presence of activated protooncogenes or activated tumour suppressor genes (Enomoto et al., 1993). It seems, therefore, that atypia is a poor prognostic factor for regression of hyperplastic to normal endometrium and a significant risk factor for progression to endometrial adenocarcinoma.

Bleeding control during GnRHa treatment was excellent. This is probably associated with blood flow changes in the uterus induced by the treatment with GnRHa (Shaw, 1996). This is an advantage over progestagens since their administration in 13–26% of the cases is associated with poor bleeding control during treatment necessitating oestrogen administration, curettage, or even hysterectomy (Ferency and Gelfand, 1989; Lindahl and Willen, 1994). The overall patient tolerance of GnRHa treatment was very good despite the presence of various climacteric symptoms. Nevertheless, progestagen administration is not asymptomatic either, since it is accompanied by side-effects such as headaches and vaginal atrophy in ~40% of cases treated (Ferency and Gelfand, 1989).

In conclusion, the treatment of non-atypical forms of endometrial hyperplasia with the GnRHa triptorelin for 6 months was associated with high regression rates (~86%) to normal endometrium. On the other hand, the results seem to be extremely poor in cases of atypical hyperplasia. Regression of hyperplasia to normal endometrium is probably due to the decreased ovarian steroidogenesis following GnRHa administration, although a direct anti-proliferative effect of GnRHa on the endometrium cannot be excluded. The presence of risk factors may contribute to the persistence of endometrial hyperplasia in some cases despite therapy. Disease persistence or progression seems to be a risk factor for adenocarcinoma development. However, bleeding control during treatment was excellent and the overall tolerance was good.

References


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