Treatment of uterine fibroids with a slow-release formulation of the gonadotrophin releasing hormone antagonist Cetrorelix

R.E.Felberbaum1,4, U.Germer1, M.Ludwig1, H.Riethmüller-Winzen1, S.Heise2, I.Buttge1, O.Bauer1, T.Reissmann3, J.Engel2 and K.Diedrich1

1Department of Obstetrics and Gynecology and 2Department of Radiology, Medical University of Lübeck and 3ASTA Medica AG, Frankfurt/Main at the Medical University of Lübeck, Germany

4To whom correspondence should be addressed: Department of Obstetrics and Gynecology, Medical University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany

A depot preparation of the third-generation gonadotrophin-releasing hormone (GnRH) antagonist Cetrorelix (SB-75) was used for preoperative treatment in twenty premenopausal patients with symptomatic uterine fibroids who were to undergo surgery. In a prospective, open, randomized setting 60 mg of Cetrorelix pamoate salt was administered i.m. on cycle day 2. Patients were randomized for a second dose of 30 or 60 mg of Cetrorelix depot, which was administered according to the degree of oestradiol suppression (<50 pg/ml) on treatment day 21 or 28. Surgery was done after 6 or 8 weeks of treatment, depending on second dosage administration. Weekly transvaginal sonography (TVS) and magnetic resonance imaging (MRI) before and after treatment was performed, for fibroid volume assessment. Sixteen patients showed satisfactory suppression of gonadotrophins and sex steroid secretion, avoiding any initial flare-up effect. In these patients a mean shrinkage rate of largest fibroid volume of 33.5% at the end of treatment could be observed according to TVS, while the mean shrinkage rate obtained after 14 days of treatment was 31.3%. In good responders (shrinkage >20%) largest fibroid volume at day 14 was ~56.7% of basic assessment. Although MRI showed minor mean shrinkage rates of only 25.4% of the initial volume, these differences in comparison to TVS assessment were not statistically significant. The avoidance of any initial flare-up in gonadotrophin secretion may explain this extremely fast reduction in fibroid size. The advantages of GnRH antagonist treatment in this indication consist in the short treatment time with a fast restoration of the ovarian function. The rate of poor responders may be reduced by using an improved slow release preparation.

Key words: depot treatment/fibroids/GnRH agonists/GnRH antagonists/uterus

Introduction

Uterine fibroids are the most frequent benign, solid tumour of the female genital tract. They occur in up to 40% of women of reproductive age. Twenty-five to fifty per cent of these women will experience symptoms due to these tumours such as menstrual disorders, anaemia, sterility, repeated abortions or premature labour (Cramer et al., 1990). Patients with multiple fibroids have to face sterility problems in ~50% of the cases (Cirkel et al., 1992) and within a population of infertile women ~5% (Buttram et al., 1981) will have intracavitory and submucous uterine fibroids (Donnez, 1996).

Fibroid development starts from a single smooth muscle cell (Townsend et al., 1970). The factors triggering this process are still unknown. Approximately 40% show abnormal karyotypes, most frequently deletions in the long arm of chromosome 7 (Pandis et al., 1991; Brosens et al., 1996). Since receptors for oestrogen and progestosterone can be detected in fibroid tissue, the sex steroids are thought to be the most important factors in the pathogenesis of uterine fibroids (Pollow et al., 1978; Wilson et al., 1980; Buchi et al., 1980; Kawaguchi et al., 1991). It is well known that uterine fibroids may react to changes in the endocrine environment, for instance fast growth during pregnancy and shrinkage after the menopause (Flicori et al., 1983; Coddington et al., 1986).

In recent years pretreatment with gonadotrophin-releasing hormone (GnRH) agonists for 3–6 months prior to surgery has become a well-established therapeutic approach. This induces a reduction in uterine and myoma size of ~50%, as well as a reduction in vascularity. These are important factors for surgical treatment of fibroids (Friedman et al., 1987; Creighton et al., 1994).

It is important to emphasize that the suppressive effects of continuous treatment with the agonists are always preceded by an initial stimulatory phase, in which luteinizing hormone (LH) and follicle stimulating hormone (FSH) are secreted in supraphysiological amounts (Lemay et al., 1980; Buchi et al., 1980; Kawaguchi et al., 1991). The factors triggering this process are still unknown. Approximately 40% show abnormal karyotypes, most frequently deletions in the long arm of chromosome 7 (Pandis et al., 1991; Brosens et al., 1996). Since receptors for oestrogen and progestosterone can be detected in fibroid tissue, the sex steroids are thought to be the most important factors in the pathogenesis of uterine fibroids (Pollow et al., 1978; Wilson et al., 1980; Buchi et al., 1980; Kawaguchi et al., 1991). It is well known that uterine fibroids may react to changes in the endocrine environment, for instance fast growth during pregnancy and shrinkage after the menopause (Flicori et al., 1983; Coddington et al., 1986). In recent years pretreatment with gonadotrophin-releasing hormone (GnRH) agonists for 3–6 months prior to surgery has become a well-established therapeutic approach. This induces a reduction in uterine and myoma size of ~50%, as well as a reduction in vascularity. These are important factors for surgical treatment of fibroids (Friedman et al., 1987; Creighton et al., 1994).

The pharmacological mode of action of the GnRH antagonists is completely different (Coy et al., 1982; Cetel et al., 1983; Loy, 1994; Rivier, 1993). Instead of down-regulation and desensitization, a classic competitive blockade of the GnRH receptors takes place on the cell membrane of the gonadotrophic cells. Without any intrinsic agonist activity of these compounds, the ‘flare up’ phenomenon is completely avoided (Reissmann et al., 1995).

In 1993, the effects of the GnRH antagonist Nal-Glu were reported. At a dose of 50 µg per kg body weight per day, administered for 3 months to patients with fibroids, shrinkage rates of >50% within the first 4 weeks were achieved (Kettel et al., 1993). For the first time, it was speculated that GnRH antagonists may be superior tools in the medical management of uterine fibroids. However, daily administrations of GnRH...
antagonists for a longer period of time seem to be poorly tolerated by the patients (González-Barcena et al., 1997). With the aim of developing a depot preparation of the GnRH antagonist Cetrorelix acetate, which had been proven to be effective and safe in the suppression of gonadotrophin secretion during ovarian stimulation for assisted reproduction, the Cetrorelix pamoate salt was synthesized by ASTA Medica AG (Diedrich et al., 1994, González-Barcena et al., 1994a,b, 1995, 1997; Felberbaum et al., 1995, 1996; Albano et al., 1996; Olivennes et al., 1994). It was demonstrated that due to its extremely low solubility (5 µg/ml H2O) this salt was able to induce a sustained suppression of gonadotrophins and was successfully tested in dimethylbenzanthracene-induced mammary cancer of the rat (Reissmann et al., 1992).

**Materials and methods**

From August 1995 our clinic was provided with the Cetrorelix pamoate salt, microparticle formulation by ASTA Medica. This is the first prototype of a GnRH antagonist depot preparation to be administered, within clinical trials, for the treatment of uterine fibroids. Cetrorelix pamoate is administered as a microparticle formulation, i.e. an amorphous compound of particles of a defined range between 80 and 120 µm in diameter. Without the need of any other matrix, 30 mg of this compound can be suspended in 2 ml of water with 84 mg mannitol, 10 mg polysorbate 80, 40 mg sodium carboxymethylcellulose and 20 mg sodium hydroxide for i.m. administration.

This prospective, open, randomized phase II study was approved by the ethics committee of the Medical University of Lübeck. Twenty premenopausal women, with symptomatic uterine fibroids gave informed consent to undergo medical treatment prior to surgery.

**Patient data**

The range of patient age was 23–45 years (mean 34 ± 5). Body weight ranged from 53 to 104 kg (mean body weight 66 ± 12 kg). A body mass index (BMI) of 40 kg/m² was not exceeded. Nineteen patients were Caucasian, one was African. All patients showed normal biochemical parameters. No patient gave a history of allergic or anaphylactoid predisposition. With the exception of 1 patient with an anemia due to (meno)metrorrhagia (Hb: 8.4 g/dl) all patients showed a haemoglobin concentration >10 g/dl. In the case of the anemic patient, dilatation and curettage was performed to rule out the possibility of an endometrial malignancy. Treatment was started as soon as the histological results were obtained. Mean cycle length was 26 ± 2 days, whilst four patients suffered from metrorrhagia. In all patients, oestradiol values >50 pg/ml during the follicular phase could be measured and only one patient showed FSH values >12 mIU/ml at the time of screening. None of them reported hormonal treatment or the use of oral contraceptives for at least 3 months before starting GnRH antagonist treatment. (Table I).

**Treatment protocol**

Fibroids had been confirmed, and uterine volume and single fibroid volume were assessed by ultrasonography and by magnetic resonance imaging (MRI).

Treatment was started by i.m. application of 60 mg Cetrorelix depot on cycle day 2. Weekly blood samples were taken for the measurement of gonadotrophins, sex steroids, Cetrorelix plasma concentrations, haematology and biochemistry controls. The fibroid volume was assessed by weekly transvaginal ultrasonography (TVS). If serum oestradiol concentrations on day 21 were <50 pg/ml a second dose of Cetrorelix was withhold until day 28, whilst concentra-

- **Treatments >50 pg/ml occasioned administration on the same day. In this open prospective study, patients were randomized to a second dosage of 30 mg or 60 mg of Cetrorelix depot. Weekly blood tests and ultrasound scans were performed for another 3 or 4 weeks depending on the day of second dosage administration. Within 3 weeks after a final MRI scan, surgical treatment was performed either by abdominal or vaginal hysterectomy or myomectomy performed at laparotomy, or laparoscopic or hysteroscopic resection. If patients showed oestradiol values >50 pg/ml within the first 2 weeks, they dropped out of the study and were treated with a conventional GnRH agonist compound (Zoladex depot; Zeneca Pharmaceuticals, ICI, Macclesfield, Cheshire, UK). According to the regulations of the ethics committee this clause was aimed at ensuring that patients who did not respond to GnRH antagonist were effectively down-regulated prior to surgery.

A good response to the Cetrorelix depot treatment was defined as a reduction of the initial uterine volume or the mean volume of up to four of the largest fibroids by >20%, as assessed by MRI prior to surgery.

**Laboratory measurements**

Serum oestradiol, progesterone and gonadotrophin concentrations were measured by enzyme immunoassay (Serono SR 1). The detection limit for oestradiol was 5 pg/ml, for progesterone 0.2 ng/ml, for LH 0.5 mIU/ml and for FSH 0.5 mIU/ml.

Cetrorelix plasma concentrations were measured in the laboratories of ASTA Medica, using the radioimmunoassay established by Schally (Csernus et al., 1990) (‘Csernus antiserum’, Gamma Counter Wallac 1470 Wizard; Berthold, Wildbag, Germany). Detection limit for Cetrorelix was 0.28 ng/ml.

All transvaginal ultrasonography (TVS) as well as bilateral uterine artery Doppler assessment of resistance indices (RI) was performed using a 7.5 MHz vaginal probe (Kranzbühler Logic 500). Sonography was performed transabdominally only in cases of huge fibroids. Uterine and fibroid volume were calculated according to the formula V = 4/3πR1×R2×R3. R = 50% of the transvaginally assessed diameter of uterus or the fibroid in one dimension (Friedman et al., 1987).

MRI was performed on an open 0.2 Tesla machine (Magnetom OPEN; Siemens, München, Germany) in the Department of Radiology at the Medical University of Lübeck. The examination procedures consisted of T2-weighted sequences in all three dimensions and one sagittal T1-weighted sequence. Volume calculation was done automatically with the established DRC system (Siemens).

**Immunohistochemical assessment of the hormone receptor concentration**

The immunohistochemical assessment of the hormone receptor concentration was performed on 4–6 µm thick paraffin wax sections. Specific antibodies to the oestrogen receptor (HK164-5K, Fa. DCS, Hamburg, Germany) and the progesterone receptor (HK163-5K) were used.

**Statistical analysis**

For statistical analysis to establish the significance of differences, the Mann–Whitney U-test was applied. This is regarded as optimal for small random groups (Lienert, 1973).

**Results**

**Adverse effects of depot Cetrorelix**

Local and systemic tolerance was excellent. In no case was a local reaction such as redness, burning, swelling or bruising observed and no allergic side-effects were noted. Eight patients
reported hot flushes within the first 4 weeks of treatment, an incidence of 50%. Four out of these eight were good responders and four poor responders, in respect of the shrinkage of the fibroids. All of these eight patients showed deep suppression of oestriadiol secretion within the first 21 days of treatment. Two of them received a second administration of Cetrorelix depot on day 21 and six on day 28.

**Treatment outcome**

Four patients with eight fibroids between them showed an insufficient suppression of oestradiol values on day 14 after the first administration of Cetrorelix depot. These ‘drop-outs’ were switched to GnRH agonist treatment for 3 months (Zoladex-Gyn-Depot; Zeneca). Three of these four showed good suppression of sex steroids by GnRH agonist treatment and successfully underwent laparotomy and myomectomy after the end of their medical treatment. Preoperative MRI was not performed in these patients, but preoperative TVS revealed only ending their medical treatment. Preoperative MRI was not performed in these patients, but preoperative TVS revealed only six open and six laparoscopic myomectomies.

Three of these four showed insufficient suppression of oestradiol values on day 14 after Zoladex injection. Since the patient demanded immediate definitive therapy, vaginal hysterectomy was performed. One patient (no. 3) heavy vaginal bleeding occurred 10 days after Zoladex injection. Since the patient demanded immediate definitive therapy, vaginal hysterectomy was performed.

Sixteen patients with 38 fibroids showed a sufficient suppression of oestradiol values (<50 pg/ml at day 14) and completed the study protocol. Eight out of these 16 received 30 mg Cetrorelix depot as second dosage, depending on their randomization. 12 patients received the second administration according to oestradiol concentrations at day 28, while four patients were treated 3 weeks after the first administration. The latter four received 30 mg Cetrorelix depot as second dosage according to their randomization.

All 16 patients were successfully operated on: one vaginal hysterectomy, six open and six laparoscopic myomectomies, three cases of laparoscopic combined with hysteroscopic ablation and finally three hysteroscopic fibroid resections.

**Uterine volume and single fibroid volume**

Uterine volumes were assessed by MRI before and after treatment, whilst the volumes of up to the four largest single fibroids in each patient were assessed by MRI and by TVS. Seven out of the 16 patients who completed the study were assessed to be poor responders, as judged by a shrinkage rate of <20% of the uterine or fibroid volume as measured above. In poor responders, reduction of uterine volume was between 0% and a maximum of 6.4%, in single fibroids between 0 and 38% (mean ± SD: 12.8 ± 13.5%). In good responders a reduction of uterine volume of between 4 and 58% could be observed (mean ± SD: 31 ± 18%); regarding single fibroids, shrinkage rates were between 12 and 60% (mean ± SD: 35.25 ± 14.8%). In those patients who received 30 mg Cetrorelix depot as a second dose (n = 8), the mean reduction of fibroid size was 20.5 ± 20%, while in those receiving 60 mg Cetrorelix depot as second injection (n = 8) a reduction of 30.4 ± 15.2% was observed. Five good responders received 30 mg Cetrorelix depot as a second injection, while four poor responders received 60 mg Cetrorelix depot as a second dose (Figure 1). According to the weekly performed TVS an overall shrinkage of largest fibroid volumes of 33.46 ± 7% (mean ± SEM) at the end of treatment was achieved. It is remarkable that at the 14th day after the first Cetrorelix depot administration, the mean reduction was in the same range (31.34 ± 7%) without major changes throughout the remaining treatment time. Within the group of good responders, largest fibroid volume on treatment day 14 was 56.74 ± 7.9% (mean ± SEM) of the initial volume before the start of treatment. There were no noteworthy changes until the end of the study when largest fibroid volume

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**Table I. Patient details (n = 20)**

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<th>Body mass index (kg/m²)</th>
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<th>Dose or 1st and 2nd depot injections (mg Cetrorelix)</th>
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FSH = follicle stimulating hormone. C = Caucasian; A = African.
in this group of patients was ~64.1 ± 11.7% of basal assessment. In the group of poor responders treatment results were 77.8 ± 8.6% of the initial volume on treatment day 14 and 70.45 ± 9.9% before surgery at the end of the study. Regarding dosage schedule, largest fibroid volume on day 14 was 61.1 ± 9.7% and 61.66 ± 11.3% at study end in the 60 mg/60 mg group, while treatment results in the 60 mg/30 mg group were 72.9 ± 7.6% and 73.9 ± 9.9% respectively (Figure 2).

**LH and FSH**

All 16 patients showed a maximum suppression of LH to concentrations <2 mIU/ml (0.66 ± 0.18; mean ± SEM) on treatment day 7. No flare-up could be observed. This deep suppression could be maintained until day 14. Between day 14 and day 21 of treatment, a slight increase in LH concentrations was observed (3.04 ± 0.58 mIU/ml). This continued until day 28 (3.49 ± 0.75 mIU/ml). Deep suppression of LH could be restored (2.06 ± 0.48 mIU/ml) by the second administration of Cetrorelix depot on day 21 or day 28. Between day 42 and study end, LH concentrations increased again, reflecting recovery of LH secretion. When comparing LH concentrations in the different subgroups of patients (‘poor responder’, ‘good responder’, 60 mg/60 mg group, 60 mg/30 mg group) a distinctly larger increase after day 42 (11.28 ± 5.4 mIU/ml at day 56) in the group of patients treated with 30 mg Cetrorelix depot as second dosage was noted (Figure 3).

FSH suppression was less pronounced than that of LH. Nevertheless, a decrease of FSH concentrations on day 7 could be seen (4.36 ± 0.52 mIU/ml). Again no flare-up effect was observed. FSH concentrations over the time of treatment were always lower than in the early or preovulatory phase of a normal cycle. Concentrations of 9 mIU/ml FSH were never exceeded. However, on day 21 concentrations were again at basal values (7.56 ± 1.3 mIU/ml). The second administration of Cetrorelix depot led to slightly lowered FSH concentrations, which increased again afterwards (Figure 4). As in the case of LH, FSH concentrations showed a distinctly higher increase after day 42 in the subgroup of patients who received 30 mg Cetrorelix depot as second injection. According to the Mann–Whitney U-test, LH suppression was significantly more pronounced on treatment days 7 and 14 (P = 0.0004), while differences on day 21, 28, 42 and 56 were not significant.

**Oestradiol concentrations**

The oestradiol concentrations of four patients were insufficiently suppressed on day 14, so they dropped out of the study. The remaining 16 patients presented mean oestradiol values on day 14 of 25.19 ± 3.85 pg/ml (mean ± SEM). On day 21, oestradiol concentrations remained under the suppression limit (47.44 ± 13.88 pg/ml). It is important to emphasize that the nadir of oestradiol concentrations, in all treated women, occurred on the seventh day of treatment. Between the 7th and 28th days of treatment, a continuous increase in serum oestradiol concentrations was observed, reaching concentrations of up to 81.38 pg/ml. As only four patients got the second administration of Cetrorelix depot on day 21, this does not interfere with oestradiol mean concentrations. Suppression of oestradiol values was re-established by the second administration on day 21 or day 28, but on a definitely higher level than before. On days 42 and 56 mean oestradiol values were 65.49 ± 19.05 pg/ml and 59.85 ± 9.52 pg/ml (mean ± SEM), respectively. Between day 56 and the day of surgery a general increase in oestradiol secretion took place (Figure 5).

Comparing mean serum oestradiol concentrations in good and poor responders, a significantly lower day 7 concentration was seen in the first group (9.50 ± 3.42 pg/ml), whilst mean values at the same time were 22.17 ± 4.85 pg/ml in the latter. Restoration of suppression due to the second administration of depot Cetrorelix seemed to be more marked in the group of good responders, showing mean oestradiol values on day 42 of 55.31 ± 25.97 pg/ml in comparison to 78.57 ± 29.44 pg/ml in the group of poor responders. As regards the dosage of second administration, restoration of oestradiol suppression appeared to be more pronounced in the 60 mg/60 mg group with mean oestradiol values on day 42 of 52.48 ± 22.92 pg/ml in comparison to 78.50 ± 31.32 pg/ml in the 60 mg/30 mg group. These differences between the two differently randomized groups of patients were not significant.

To analyse the influence of pretreatment oestradiol levels, the oestradiol concentrations throughout the treatment period were compared for patients with pretreatment serum values of <50 and >50 pg/ml. Although the mean values of oestradiol were clearly different, these variations were only significant at day 7 (P = 0.0227).

**Progesterone concentrations**

The nadir of progesterone concentration following depot Cetrorelix treatment was seen on day 7 (mean values 0.76 ± 0.14 ng/ml). Up to day 14, values increased to 2.42 ± 1.38 ng/ml, declining between day 14 and day 28. At this time, mean progesterone concentration was ~1.66 ± 3.84 ng/ml. Between day 28 and day 42 of treatment, mean values rose to ~3.84 ± 1.5 ng/ml (Figure 6). Mean progesterone concentrations differ between patient groups. Progesterone concentrations in good responders were constantly low until day 28. After this time, concentrations rose up to postovulatory values of 5.39 ± 2.52 pg/ml.
Figure 2. Mean reduction in volume of largest fibroids as percentage of pretreatment value at screening (transvagal ultrasound) following two doses of depot Cetrorelix.

Figure 3. Mean serum luteinizing hormone (LH) concentrations (mIU/ml) following Cetrorelix treatment.

Figure 4. Mean courses of serum follicle stimulating hormone (FSH) concentrations (mIU/ml) following Cetrorelix treatment: all patients.

ng/ml. Mean progesterone values in poor responders showed astonishingly high values at treatment day 14 (3.99 ± 3.18 ng/ml). Between day 14 and day 28 progesterone values fell in these patients and rose again afterwards. Three poor responders showed postovulatory concentrations after the second administration of Cetrorelix depot, one on day 42 and two on day 56 of treatment. After the second administration of depot Cetrorelix, the 60 mg/60 mg group showed constant low values up to treatment day 28, with mean concentrations

Figure 5. Mean serum oestradiol concentrations (pg/ml) following Cetrorelix treatment: all patients.
of 0.93 ± 0.18 ng/ml at that time. Nevertheless, mean progesterone values in the 60 mg/30 mg group did not differ significantly. No significant differences could be observed between mean progesterone concentrations in relation to oestra-diol concentrations, at start of treatment.

Cetrorelix plasma concentrations

Within 1 h after the first dose of depot Cetrorelix (60 mg), mean plasma Cetrorelix concentrations were 18.6 ± 1.98 ng/ml (mean ± SEM). Within 6 days, concentrations fell to ~5.61 ± 1.02 ng/ml. On treatment day 14, mean plasma concentrations were ~3.06 ± 0.28 ng/ml and fell by day 21 to mean values of 1.83 ± 0.17 ng/ml. Following the second administration of depot Cetrorelix in four patients on treatment day 21, 1 h after administration, a mean value of 12.24 ± 1.88 ng/ml was obtained. On treatment day 28, mean values were 1.57 ± 0.24 ng/ml before and 19.25 ± 1.75 ng/ml 1 h after administration of Cetrorelix depot. On day 42, mean values of plasma Cetrorelix concentrations fell to ~2.88 ± 0.34 ng/ml and were ~1.93 ± 0.21 ng/ml at day 56. As regards the four ‘drop out’ patients, one very obese patient showed extremely low Cetrorelix plasma concentrations 1 h after injection of 60 mg compound (patient no. 3: 1.72 ng/ml), while the remaining three showed normal initial plasma concentrations of the GnRH antagonist administered (Figure 7).

Discussion

Oestradiol appears to enhance the rate of growth of leiomyomata and to act as a growth factor (Friedman et al., 1987). Observations that sustain this hypothesis are the increase in size of fibroids in pregnancy and regression of these tumours after the menopause (Frankel et al., 1975). Histological examinations demonstrate endometrial hyperplasia at the edge of each fibroid, indicating an oestrogenic microenvironment for these tumours (Deligdish et al., 1970; Farrer-Brown et al., 1970). Therefore, preoperative conservative treatment with GnRH agonists could be established. Iatrogenic, temporary and fully reversible hypogonadotrophic hypogonadism was proposed to induce shrinkage of fibroid volume as well as a diminution of vascularization to ease the surgical procedure to a certain extent and to allow less invasive techniques such as a laparoscopic or hysteroscopic surgery (Coddington et al., 1986; Maheux et al., 1987; Perl et al., 1987; West et al., 1987; Creighton et al., 1994). An average shrinkage of uterine volume of ~50% over 3 months is reported to be normal (Friedman et al., 1993). Unfortunately, volume reports differ substantially regarding single fibroids. Mean shrinkage rates of single fibroid volume of ~27%, but also ‘non-responder’ or even increases in volume under full treatment have been described (Friedman et al., 1987; Cohen et al., 1990). After ending the treatment, fibroids regain their initial volume if surgery is not performed within 3 months (West et al., 1987). It is important to emphasize that the indication for this expensive therapy is still a matter of debate. At present, only patients with anaemia due to severe uterine bleeding and patients with submucous fibroids in whom a hysteroscopic operation is planned, are widely accepted as candidates for this regime (Donnez, 1996). Nevertheless, the uterine fibroid works as a model for treatment of a sex steroid-dependent tumour by hormonal deprivation.

The theoretical advantage of GnRH antagonist treatment instead of agonist medication would be that it avoids any flare-up effect. The feasibility of this treatment by daily injections has been described (Kettel et al., 1993; González-Barcena et al., 1997). The data presented here are the first results of treatment with a GnRH antagonist slow release preparation, in patients with uterine fibroids.

Regarding the gonadotrophin concentration under the treatment with the antagonist, it was remarkable that the FSH concentration increased after a slight suppression in the begin-
Table II. Oestrogen receptor status and surgical procedure performed in patients with fibroids following depot Cetrorelix treatment

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Visit at which 2nd injection given</th>
<th>1st/2nd dose (mg)</th>
<th>Response to treatment (MRI-assessed shrinkage)</th>
<th>Oestrogen receptor expression (%)</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
<td>60/60 good</td>
<td>good</td>
<td>50–80</td>
<td>vag. hyst.</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>60/60 good</td>
<td>good</td>
<td>50–80</td>
<td>lap. hystc.</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>60/30 good</td>
<td>bad</td>
<td>50–80</td>
<td>lap. hystc.</td>
</tr>
<tr>
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<td>bad</td>
<td>50–80</td>
<td>lap. hystc.</td>
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<td>bad</td>
<td>50–80</td>
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</tr>
<tr>
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<td>good</td>
<td>50–80</td>
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<td>bad</td>
<td>50–80</td>
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</tr>
<tr>
<td>14</td>
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<td>good</td>
<td>50–80</td>
<td>lap. hystc.</td>
</tr>
<tr>
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<td>good</td>
<td>50–80</td>
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</tr>
<tr>
<td>16</td>
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<td>good</td>
<td>50–80</td>
<td>lap. hystc.</td>
</tr>
<tr>
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<td>50–80</td>
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</tr>
<tr>
<td>18</td>
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<td>19</td>
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<td>50–80</td>
<td>lap. hystc.</td>
</tr>
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<td>20</td>
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<td>60/30 good</td>
<td>good</td>
<td>50–80</td>
<td>lap. hystc.</td>
</tr>
</tbody>
</table>

MRI = magnetic resonance imaging; lap = laparotomy; hystc. = hysteroscopic resection; lapsc. = laparoscopic resection; vag. = vaginal hysterectomy.

Figure 8. Uterus myomatosus before (a, 454 cm³) and after Cetrorelix depot treatment (b, 226 cm³); shrinkage rate of 50.2%.

ning. On the 21st treatment day, values were reached which met or exceeded those from the beginning of the study. This was in accordance with the results from ovarian stimulation (Felberbaum et al., 1996). However, no exogenous FSH was given in this study. Methodological errors cannot be ruled out because immunoreactive, but not bioactive, FSH was measured. The LH values, however, were significantly suppressed. A statistically significant difference of LH and FSH values on the different days was proven for treatment days 7 and 14. This was in accordance with the data of Kettel et al. (1993). A possible explanation may be a proposed FSH releasing factor (Schally et al., 1971) or a dose-dependent suppression of LH and FSH by the antagonist (Behre et al., 1994).

The oestradiol concentration was suppressed to the expected value of <50 pg/ml in all 16 patients during the first treatment phase. In the second treatment phase, the oestradiol concentrations were higher and reached values of 65.49 ± 19.05 pg/ml and 59.85 ± 9.52 pg/ml on the 42nd and 56th treatment day respectively. This explains the disappearance of withdrawal symptoms in all patients during the second treatment phase. This is in accordance with the so called ‘add-back’ therapy in agonist treatment regimens (Maheux et al., 1991), and show that it should be feasible to maintain a low oestradiol secretion under adjusted GnRH antagonist treatment so that a therapeutic suppression occurs without withdrawal symptoms (Bouchard et al., 1990).

Since three patients showed postovulatory progesterone values in the second treatment phase, it may be postulated that reactivation of ovarian steroid biosynthesis is accelerated compared to an agonist treatment. This is also shown by the phenomenon of a normalization of the steroid concentrations within a few days after the end of treatment, compared to an agonist regimen (Gordon and Hodgen, 1993).

The plasma concentrations of Cetrorelix show that the depot preparation used in this protocol needs improvement, since the high plasma concentration within the first hour after application (18–20 ng/ml) fell to a quarter of that value after 1 week. The dose needed for hormonal castration in men was calculated to be 10 ng/ml (Behre et al., 1995). Although concrete reference values for women are not yet available, mean serum concentrations of 1.56 ng/ml as observed on day 28 of treatment may be too low (T. Reissmann, personal communication). Using a preparation with a faster release, the necessary dosage could be reduced. This objective could be achieved using salts with an intermediate solubility compared to acetate or pamoate, or by using polymeric matrices as in the agonist depot preparations (Runnebaum and Breckwoldt, 1992). For these preparations, problems of composition must
be solved, since agonists have a far more complex molecular structure compared to antagonists and matrix load would have to be ~10-fold higher than in the case of agonists.

Four patients showed an insufficient hormonal suppression on treatment day 14 (oestradiol >50 pg/ml). One patient with a body weight of 104 kg showed a Cetrorelix plasma concentration of 1.72 ng/ml on this day. It was considered that in this patient depot Cetrorelix could not be administered i.m. despite the use of a long injection needle (Terumo®). The other three patients showed a Cetrorelix plasma concentration in the same range as the other patients. This is in accordance with results from animal experiments (Reissmann et al., 1996). These rates would be comparable with the incidence of insufficient suppression of the pituitary gland under GnRH agonist treatment (Filicori et al., 1988). However, the dropout rate of 15% in this study seems to be far too high for clinical use of this preparation.

The cut-off level for sufficient reduction of mean fibroid volume was 20%. Therefore, seven patients were poor responders with a total reduction of 0 to 6.4% and a reduction of the single fibroids ranging from 0 to 38%. In the group of the good responders, the uterine volume was decreased by a mean of 31% according to the MRI evaluation. This is below the rate of reduction using agonist preparations (Friedmann et al., 1993). However, a reduction of >50% was achieved in single cases (Figure 8). The reduction for the single fibroids ranged from 12 to 60% (mean ± SD: 35.25 ± 14.75) and was in the expected range for an agonist protocol. Transvaginal Doppler assessments of both uterine arteries of each patient at each visit showed no significant increase of RI over the treatment period. The RI remained in the range to be expected for benign uterine tumours, between 0.57 and 1.0 (Kurjak et al., 1991). This could indicate that fibroid vascularization is not diminished by GnRH antagonist treatment despite the observed fibroid shrinkage. However, blood loss during surgery was low and fibroid tissue was thought to be definitely softer than for cases without pretreatment.

The great advantage was the short treatment time necessary to obtain shrinkage of the fibroids. With an agonist preparation, ~14 days are lost for the initial flare-up effect and the time to obtain shrinkage of the fibroids. With an agonist preparation, ovarian function can be restored in shorter times compared to a treatment with a GnRH agonist depot. GnRH antagonists obviously open up new avenues to a short-term preoperative medical treatment for uterine fibroids. However, 15% of our study patients dropped out, as they did not respond to the first depot injection, in terms of a suppression of serum oestradiol secretion and 37% of those who completed the study responded poorly in terms of a reduction in uterine/fibroid volume. However, this rate can be expected also in agonist treatment regimens. Before this kind of depot preparation can be used in malignant hormone-dependent disorders, a more reliable suppression must be achieved. A technical improvement of the biopharmaceutical preparation may be helpful in avoiding the disadvantages observed in this study.

Acknowledgements
We thank the company Asta Medica for kindly supplying Cetrorelix depot and help with the organization of this study. We also thank the Asta Medica Central Laborotories and especially Dr P.Romeis for the measurement of Cetrorelix concentrations in plasma.

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Cetel, N.S., Rivier, J., Vale, W. and Yen, S.C.C. (1983): The dynamics of gonadotropin hormone-releasing hormone analogue used to treat uterine leiomyomata lead to an overall reduction in fibroid size of 50% after 3 months, in our experience of oestrogen receptors has been described (Kavagucli et al., 1991).

To summarize our results, it has been shown that the preoperative treatment of fibroids using Cetrorelix pamoate microparticle preparation is feasible and highly effective in most patients. A maximum reduction could be achieved within 14 days of treatment, which is faster than using an agonist preparation. Ovarian function can be restored in shorter times.


Received on July 17, 1997; accepted on February 26, 1998.