Effectivity of GnRH analogue therapy in the patient with endometriosis

Summary of Ph.D. thesis

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I. Introduction

Infertility is usually defined, for a given couple, as the inability to achieve pregnancy within a reasonable duration. This time lag, two years in the guidelines provided by the World Health Organization (WHO), is often shorter in clinical practice, depending both on the impatience of the couple and on the celerity of the physician. Such a condition affects between 15% and 20% of the population in most countries, both developed and developing. Among these couples, only a small proportion are affected by complete infecundity, i.e. sterility. These couples usually comprise between 3% and 5% of the population of reproductive age. In developed countries, the average fecundability (the "per cycle" probability of conception) generally fluctuates around an average value of 30%. Although the prevalence of unexplained infertility is decreasing, since the clinical and biological diagnostic procedures are becoming more efficient, conditions in which no factor explaining infertility is found in either the man or the woman account for between 5% and 10% of the cases in the varying surveys. Among the female factors, ovulation disorders (whatever their nature) and tubal alterations are the most prevalent conditions. In the great majority, partial or complete tubal alterations are the consequences of pelvic inflammatory disease following sexually transmitted diseases. Bacterial vaginosis associated with Gardnerella vaginalis, genital mycoplasmas and several anaerobic species, including Mobiluncus is the most prevalent cause of vaginal discharge, another cause of infertility. Over the last 30 years, there has been a large increase in the number of infertile patients found to have endometriosis. It is uncertain whether this is an actual increase or is simply a reflection of the more frequent use of laparoscopy in the investigation of the infertile couple.

Endometriosis is a well-known disease in women of reproductive age. The functioning endometrial gland and stroma are situated outside the uterine cavity, and may be accompanied by pains in the small pelvis, infertility, dysmenorrhoea, dyspareunia and adnexal tumours. It is a benign, but usually persistent and progressive disease, second in incidence to myoma. In 95% of the cases, it occurs in women between the menarche and menopause, whereas in the postmenopause a relationship seems to be evident with the oestrogen intake and hormone replacement therapy. Little is known about the real incidence. While an incidence of 20-50% is reported in the course of examinations by laparoscopy in consequence of infertility, an incidence of 15-25% is mentioned during gynaecological operations performed on account of pain in the small pelvis. Endometriosis of the small pelvis is typically a disease of the age groups of 25-30, while

the extragenital form affects mostly the age group 35-40. Although one-third of the patients are free of symptoms, in endometriosis the acute and chronic pain in the small pelvis is the most frequent complaint, which appears during the menstrual cycle and is associated with dysmenorrhoea and dyspareunia. The pain may be constant, on one or both sides, radiating towards the vagina, the groin, the buttocks or the perianal region.

In most cases, laparotomy nowadays has replaced by operative laparoscopy, which plays the main role in the primary diagnosis of endometriosis, in the course of which the changes typical of endometriosis become apparent. In the diagnosis of the disorder, we can directly vizualise the classic endometriotic implant characterized by brown or black pigmentation and fibrosis, while direct biopsy can be performed on the non-characteristic lesions, which facilitate the true diagnosis. Originally straightforward and easy, the diagnosis has developed into an art which requires a complete knowledge of the symptomatology of the various aspects, and above all an in-depth interpretation of all of the peritoneal anomalies.

II. Aims of the investigation

1. To determine the incidence of endometriosis due to infertility and examine the efficacy of gonadotropin releasing hormone (GnRH) analogue therapy in the treatment of the disease.
2. To compare the efficacy of two GnRH analogues, nafarelin (Synarel, Syntex) and triptorelin (Decapeptyl-Depot, Ferring), and their side-effects during a 6-month course of therapy and for another 6 months after the cessation of treatment.
3. To compare the efficacy of assisted reproductive technology, intrauterine insemination (IUI) after GnRH analogue therapy in patients with endometriosis and patients who are free of this disease.
4. To create a treatment protocol for infertile patients who have endometriosis.

III. Patients, materials and methods

On admission, a thorough gynaecological examination was performed in all of the patients included in the studies (colposcopy, cytology and bimanual, together with breast examination). Three months prior to the beginning of the trial, the duration of the menstrual cycle was found to be between 24 and 35 days. Each infertile patient complained of dysmenorrhoea or dyspareunia. None of them was aware of any blood-clotting disturbance. The patients were given information on the need for laparoscopy, the administration of the required drugs and their potential adverse effects. They were asked to keep a therapy record, noting any complications, any symptoms or complaints, and details on the drugs taken. In addition, hyperandrogenic symptoms, mood swings and libido, together with any alteration in the frequency of headaches were noted. During the trial, patients in all groups were asked not to take any hormone products. The degree of intensity, frequency and tolerance of hot flushes were recorded on a visual analogue scale, whose data was based on the patients' complaints. The scale ranged from 0, meaning no pain or discomfort, to 10, at which the symptoms are intolerable. Each month we noted the body weight and blood pressure, and evaluated the small-pelvic pain according to the results of a physical examination. No patient from either group took any steroids, and the medical history indicated that no patient was pregnant or lactating in the 3 months prior to the trial. We performed videolaparoscopy with chromopertubation prior to the start of the therapy. All the laparoscopies were performed under general endotracheal anaesthesia with a 10 mm diameter 30° laparoscope; in some patients, a biopsy was performed for histological confirmation of endometriosis. Where the diagnosis of endometriosis was uncertain during laparoscopy, histological examination of the biopsy sample confirmed the disease or disproved it. When endometriosis was diagnosed laparoscopically and/or histologically, the therapy was initiated in the first menstrual cycle after the operation.

Several classification methods are available for defining the extent and the consequences of the disease, as well as for assessing the efficiency of the surgical or drug therapy. The score system of the American Fertility Society (AFS), modified in 1985, is currently the most widely accepted, and our classification was made on this basis. The obtained scores were utilized to divide the patients into four stages.

III. 1. Nafarelin study

We performed 122 laparoscopies, indicated by infertility, chronic pain in the small pelvis, dyspareunia or ovarian cyst, with endometriosis as the underlying cause in 30 patients (25%). Following laparoscopy, all the 30 patients involved in our study were given GnRH treatment with nafarelin for 6 months, beginning from the first day of the first menstruation after the surgery. The initial dose of the drug was 2 x 200 μg per day intranasally, applied in both nostrils in turn in order to avoid the problems resulting from the possible local irritation. The use of nasal drops was not recommended between 1 hour before and after the administration of the drug because of vasoconstriction and resulting absorption failure. In the event of penetrating bleeding, the daily dose was raised to 800 μg.

At the onset of the treatment, as well as at the end of the first, third, sixth, ninth and twelfth months, we checked the severity of dysmenorrhoea, dyspareunia and pain in the small pelvis, relying upon the patient's complaints and the examination findings showing the extent of pressure sensitivity of the small pelvis.

Within 2-4 weeks following the end of the drug therapy, control laparoscopy was carried out to examine the activity and the extent of the disease, taking the AFS classification into consideration. After the examination, we evaluated the changes in dyspareunia, in dysmenorrhoea, in pain in the small pelvis and in pressure activity.

III. 2. Nafarelin and triptorelin study

133 patients with, laparoscopically-diagnosed endometriosis were treated with GnRH analogues. The efficacy and side-effects of nafarelin and triptorelin were compared during a clinical study of a 6-month course of treatment with a 6-month follow-up period. At the onset of the treatment, as well as after every month of the treatment cycle and the seventh, ninth and twelfth months, blood was taken to determine the serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and 17β-oestradiol. There were 30 patients in the nafarelin group and 103 in the triptorelin group. In the first group, the patients' ages ranged from 18 to 42 years of age (average age 31 years), while in the second they ranged from 19 to 45 (average 32 years). In the nafarelin group, 2 patients were given danazol, while in the triptorelin group, 11 patients were given progestogen and/or danazol (but more than 6 months prior to the start of the treatment).

The initial dose of nafarelin was 400 μg, which was administered twice daily as an intranasal insufflation in both nostrils in turn. When breakthrough bleeding occurred, the dose of the drug was raised to an amount no greater than 800 μg. The use of nasal drops was not recommended before or after the nasal insufflation so as to avoid the occurrence of local vasoconstriction and a consequential absorption disorder. Each month, a dose of 3.75 mg triptorelin was administered intramuscularly (given in the deep muscle layer).

III. 3. Triptorelin and ovulation induction study

At our Department ovulation induction and homologous arteficial intrauterine insemination (HIUI) were performed, after GnRH analogue therapy, on 33 patients suffering from laparoscopically diagnosed endometriosis. The patients' ages ranged from 25 to 32 years of age (average age 28.3 years), while their body weights ranged from 65 to 80 kg (average 75.6 kg). One patient was given danazol, but this was more than 6 months prior to the start of the treatment. Prelaparoscopic investigations included evaluation of the basal body temperature, and the vaginal discharge for microbiological culture. Blood was taken to determine the serum levels of FSH, LH, prolactin, testosterone and 17β-oestradiol on day 3 of the menstrual cycle, and again on day 21 of the cycle, to assess the progesterone level. The hormones were measured by a chemiluminescent immunoassay with a DPC Immulite instrument. In the andrological examination of the partner, a spermiogram was taken and bacteriological testing of the seminal fluid and a postcoital test were performed. 3.75 mg triptorelin was administered intramuscularly each month for 6 months. 21 days after the last injection was given, ovulation induction was started according to the monofollicular protocol. 50 IU Puregon (pure FSH) was given daily for 2 days, and then from the third day, 1 ampoule of Humegon (75 IU FSH, 75 IU LH) was administered intramuscularly. On the fifth or sixth day of the stimulation, transvaginal ultrasonographic (TUS) examination was carried out. If the size of the dominant follicle and/or thickness of the endometrium did not reach the required level, the administration of Humegon was continued and the TUS examination was performed daily. If the dominant follicle reached a size of 20 mm and the endometrium was thicker than 9 mm (consisting of 3 layers), 10.000 IU hCG was given for luteinization after the serum level of oestradiol was determined. Wherever there was a danger of ovarian hyperstimulation, luteinization was not carried out. An intrauterine HIUI was performed 36

hours later. For homologous insemination, the concentration of sperm was determined from the homogenized ejaculate. The washing and enrichment of the sperm was carried out via "swim-up" technology. If the concentration reached $40x10^6$ /ml, 3 ml of washing fluid (Spermfit, BIOMEDICAL) was added to 1 ml of ejaculate. If the concentration did not reach $40x10^6$ /ml, 2 ml of washing fluid was added to 1 ml of ejaculate, the mixture was then centrifuged at 400 g for 10 minutes and the supernatant was drawn off. 1 ml of the medium was layered over a precipitate, care being taken not to agitate the precipitate. The material was incubated at room temperature for 45 minutes, and the sperm concentration, motility characteristics, the percentage, and the percentage of the normal forms were then repeatedly evaluated. This procedure was carried out after the administration of hCG, but before the HIUI.

III. 4. Ovulation induction and body mass index study

At our Infertility Outpatient Unit, 1144 married couples who attended between 1992 and 1998 requested donor artificial intrauterine insemination (DIUI) treatment. After a thorough history-taking, the infertility examination was carried out on the basis of the criteria given by the WHO: determination of the prolactin and progesterone levels of the serum on days 21-23 of the menstrual cycle, hysterosalpingography and examination of the husbands. We excluded the possibility of endometriosis via the lack of typical symptoms; we did not perform laparoscopy. The Fallopian tubes of the wives were passable, the serum prolactin scores were in the normal range (below 580 mU/l), and their cycles proved to be ovulatory (serum progesterone above 19 nmol/l). Azoospermia or severe oligozoospermia (sperm concentration below 5 million/ml) was found in the husbands. The body mass index (BMI) was determined on the basis of the formula body weight (kg) / body height (m^2). For extremely thin or obese patients, endocrinological examination was required in order to exclude the possibility of endocrine or metabolic diseases. During the preparation for DIUI, superovulatory treatment (clomiphen and gonadotropin) was carried out and the cycles of the wives were monitored. In the course of appropriate follicular maturation, which was proved by ultrasonographic folliculometry and by determination of the serum oestradiol level, 7500 IU hCG was injected to provoke follicular rupture, and 24 hours later the DIUI was performed. The subsequent pregnancy was proved by immune pregnancy testing and TUS.

IV. Results

IV. 1. Nafarelin study

Before the start of the therapy, 20 of the 30 patients were in stage III according to the score system and 10 in stage II. After the treatment, 5 patients were in stage III, 6 in stage II, 7 in stage I and 12 in stage 0. According to the total AFS score system, which takes into consideration the adhesions, too, recovery was achieved in 11 cases and a partial improvement in 19 cases. Control laparoscopy revealed the total disappearance of the endometrial foci in 21 cases, partial disappearance in 8 cases, no change in 1 case and no aggravation in any of the cases. In the course of the study, a considerable improvement in dysmenorrhoea was found, with entire cessation in 22 cases. The pain in the small pelvis was considerably alleviated, or disappeared following a few aggravations in the beginning. There was a marked improvement or cessation of dyspareunia according to the subjective assessments of patients. From the beginning of the treatment until the end of the second month, there was a discontinuance in menstruation and no bleeding occurred throughout the course of the treatment. Following the cessation of the therapy, the normal menstruation cycle was restored within 56 days in 28 cases. Due to amenorrhoea in 2 cases, bleeding was induced with Norethisterone following day 56. Hot flushes gradually became more intensive from the third week of the treatment; in a few cases headaches, and in 2 cases numbness of the upper limbs with pain were found as side-effects. There was no need to interrupt the study before due time in consequence of side-effects or unexpected complications.

IV. 2. Nafarelin and triptorelin study

No significant differences were observed between the groups in the frequency of hot flushes during the 6-month course of treatment with a 6-month follow-up period. The hot flushes started in the first month of the analogue therapy, and occurred several times a day; were mild at that time, but as the therapy progressed, the number and intensity increased. The number and intensity of the hot flushes were highest in the third month of the therapy and from the fifth month onwards a decrease in number was noticed. In the first month following analogue therapy, reductions were observed in both their number and their intensity. The hot flushes

completely disappeared from the second month on following the therapy. In the first month after the start of the medical therapy, the symptoms characteristic of menopause (colpoxerosis, nervousness, mood swings, and reductions in libido and in the size of the breasts, accompanied by hot flushes) appeared due to hypoestrogenism. As regards side-effects no significant difference was found between the two groups.

There was no significant difference between the serum hormone levels in the two groups during and after the analogue therapy. We found that the GnRH analogue therapy decreased the serum FSH and LH concentrations, and the oestradiol level in all patients was in the postmenopausal range; after the therapy, all the values were within the normal range. At the end of the medical therapy, the ovaries were no longer inhibited, so the menopausal symptoms gradually became milder and eventually vanished. After an initial exacerbation the symptoms characteristic of endometriosis showed an improvement in both groups as compared to those prior to the start of the treatment, which was a consequence of the effect of the analogue therapy. We found no significant complications in either therapy group. When the control laparoscopy was performed later, a significant improvement in the recovery from the disease was inferred. In the nafarelin group, 20 patients were in stage III and 10 in stage II at the beginning of the treatment. However, at the end only 5 patients were in stage III, 6 in stage II, 7 in stage I and the remaining 12 in stage 0. In the triptorelin group, prior to the start of the treatment 20 patients were in stage IV, 46 in stage III, 31 in stage II and 6 in stage I, but after the treatment only 8 patients were in stage IV, 20 in stage III, 22 in stage II and the remaining 26 in stage 0. A marked improvement was also seen in those cases where the stage did not change after the treatment, as compared to the stage at the beginning of the treatment.

IV. 3. Triptorelin and ovulation induction study

The serum hormone levels were determined on days 3 and 21 of the menstrual cycle, within 2 months prior to the laparoscopy. In each case, normal hormone levels were detected. The laparoscopy revealed that 10 patients were in stage III, 18 in stage II and the remaining 5 in stage I. Those patients whose tubes were shown to be penetrable via chromopertubation were included in the trial, while those with one or both Fallopian tubes occluded were excluded from the trial. GnRH analogues were naturally prescribed for the treatment of endometriosis. The andrological analysis in each case found normozoospermia. In 4 cases, the

bacteriological test detected the presence of a pathogen, so targeted antibiotic therapy was given in accordance with the antibiogram. In 1 case, after the control test, targeted antibiotic therapy was repeatedly given until a negative result was attained.

In the first month of the induction treatment, 5-8 (6.8 on average) ova reached a size of 20 mm up to day 12 of the induction, which is in part due to the rebound effect following the inhibition. The follicle size ranged from 20 to 28 mm (24.4 mm on average). The intervention resulted in pregnancy in 15 (45%) cases, 3 of them being twin pregnancies. In 1 case, a spontaneous abortion took place in week 15 of pregnancy.

IV. 4. Ovulation induction and BMI study

The BMI of the women involved in the study varied between 16 and 36. On this basis, they were divided into 4 groups: A: 16-19 (thin), B: 20-24 (normal weight), C: 25-27 (moderately overweight) and D: 28-36 (obese). Most of the women were in the normal BMI group. In the course of the superovulatory treatment, the induction was inefficient in 96 cases, and satisfactory follicle development did not occur. The risk of unsuccessful superovulatory treatment rise in a parallel with the shift from the ideal body weight (A: 1.5, C: 1.4, D: 2.7).

As a result of DIUI carried out between 1992 and 1998, 412 pregnancies occurred, i.e. a success rate of 36%. Among the 412 pregnancies there, were 376 singlets, 29 twins, 6 triplets and 1 quintuplet. In the latter case, at the request of the couple, pregnancy reduction was performed in gestational week11, resulting in 2 live embryos. In spite of careful treatment and nursing, premature labour occurred in week 32 of the pregnancy. Caesarean section was performed due to placenta praevia and live male twin foetuses weighing 1230 and 1390 g were delivered. From the pregnancies classified on the basis of the BMI, it can clearly be seen that DIUI can be applied most successfully in the case of a normal body weight (42%), whereas the pregnancy rate in overweight patients is only 21%.

V. Discussion

V. 1. Nafarelin study

30 patients were involved in the study, with control laparoscopy in each case. The regular menstrual cycles discontinued in the second month of the treatment. The adhesions and the peritoneal lesions were taken into consideration. A tremendous improvement occured in the symptoms. Dyspareunia ceased in 22 cases (73%). During therapy with nasal nafarelin, Henzl et al. found that the dyspareunia was eliminated in 87%, whereas in the control group it was eliminated in 69% in response to oral danazol treatment. The pelvic pain lessened considerably or ceased in response to nafarelin, similarly as following treatment with danazol. Within 6 months following the treatment, 7 pregnancies occurred (23%), which was similar to the 28% found by Henzl et al.

V. 2. Nafarelin and triptorelin study

There was a noticeable decline in the symptoms of endometriosis. Dyspareunia was eliminated in 73% of the nafarelin group, as compared with 82% in the triptorelin group. Berquist et al. found that dyspareunia disappeared in 87% of the patients following triptorelin therapy, as compared with a 52% decrease in the control group, where a placebo was given. These results are similar to the findings of Gardo et al. who observed a clear reduction or complete disappearance of the small-pelvic pain following nafarelin or triptorelin therapy together with danazol therapy. Similar results were obtained by Regidor et al., who reported a 20% pregnancy rate after buserelin acetate therapy. Seven (23%) patients in the nafarelin group became pregnant, as did 22 (21.4%) patients in the triptorelin group within 6 months following the treatment.

V. 3. Triptorelin and ovulation induction study

During the 6-month treatment with analogues, certain side-effects due to hypo-oestrogenism emerged some 2-3 weeks after the first triptorelin injection. The menopausal symptoms gradually increased up to months 4 and 5 of the treatment, and a slight reduction was noticed in month 6. The ovulation induction therapy was started according to the monofollicular

protocol, on day 21 of the cycle after the last analogue injection was given. In the first month of the induction treatment, 5-8 (6.8 on average) ova reached a size of 20 mm. This number is significantly different from the numbers of mature follicles (3.9 and 4.2) obtained after long-term therapy with GnRH analogue and hMG by Schmutzler and Leyendecker, and slightly lower than the results of Frydman, who obtained on average 8.4 ova after the long-term protocol. Hyperstimulation was not observed during the trial, so luteinization was performed in each case. After homologue artificial therapy, 15 (45%) patients became pregnant, 3 of these cases involving twins. This compares to efficiency rates of 25% and 27% following embryo transfer obtained by Leyendecker and Frydman, respectively. The 45% success rate is probably mostly due to the young age of the patients, the rebound effect following inhibition and the fact that no other causes of infertility apart from endometriosis were observed. This may be compared with the report by Koloszár, whose success rate was 36% following donor insemination, but in this study the patients' body weight was not ideal. When the patients' weight was normal, the success rate was similar (42%), but in the low and high body weight groups the rate was lower (28% and 21%). To sum up, the above course of treatment (6-month GnRH analogue therapy, the ovulation induction following the monofollicular protocol and HIUI) can be applied successfully in the treatment of infertility caused by endometriosis.

V. 4. Ovulation induction and BMI study

It is well known that ovulatory disorders are more frequent in lower and higher body weight groups. Furthermore, the efficiency of ovulation induction with clomiphen citrate can be considerably enhanced of decreasing a pathologically high body weight, or increasing a too low weight, towards the ideal condition. The ideal body weight can ensure a favourable interior environment for the function of the endocrine system; additionally, a pathological body weight may play a role in luteal failure. In order to maintain the ideal body weight, the intact functioning of certain areas of the hypothalamus is necessary. It has been found in animal experiments that, following lesions of the medial preoptic part of the hypothalamus, the body weight increases and an ovarian malfunction occurs. Furthermore, in female animals, oestrogen withdrawal by castration leads to an increased food intake. The inhibitory effect of oestrogen on nutrition takes place through the neuropeptide-Y and the galanin peptidergic system. When a total of 1144 infertile women were treated by DIUI,

unsuccessful ovulation induction was found in 96 cases. The obese women (BMI: 28-36) had a relative risk of unsuccessful ovulation induction of 2.7 (95% CI = 2.1-3.4) as compared with women with a lower or normal body weight (BMI: 20-24). The effect was smaller in women with a BMI of 25-27 or <19 (RR = 1.4, 95% CI = 0.9-2.1 and RR = 1.5, 95% CI = 0.8-2.5, respectively). During DIUI treatment, 412 pregnancies occurred. The pregnancy rate achieved by insemination was 28% (50 pregnancies in 178 cases, BMI 16-19), 42% (251/599, BMI 20-24), 33% (98/286, BMI 25-27) and 21% (19/81, BMI 28-36), in the different BMI groups.

VI. Conclusions

Nafarelin and triptorelin are synthetic GnRH analogues which are 200 times as effective as the endogenous protein. They stimulate the release of LH and FSH from the anterior lobe of the pituitary, but this effect shows a gradual decrease in continuous administration as a result of desensitization of the pituitary due to the down-regulation of the receptors. The treatment aims at the pharmacological manipulation and changing of the milieu in the small pelvis. In response to continuous administration, nafarelin and triptorelin inhibit the pituitary - ovary axis and the evoked hypooestrogenic condition proves to be very efficient in the therapy of the endometriosis of the small pelvis, with rapid decreases pain and other symptoms. The induced oestrogen deficiency condition is tolerated by the patients quite satisfactorily.

Results of the investigation

1. We sought to explain the incidence of endometriosis due to infertility in our region, the clinical application and efficiency of nafarelin in cases of endometriosis diagnosed during laparoscopy, and the decline in activity and expansion of the disease in the course of the 6-month therapy. We performed 122 laparoscopies in the investigation of infertility and found endometriosis to be the underlying cause in 30 patients (25%). After treatment of the adhesions and the peritoneal lesions was taken into consideration, there was a marked improvement in the symptoms.

2. We compared the clinical applicability, the efficacy, and the usual and unexpected side-effects of two GnRH analogues, nafarelin and triptorelin, and the reduction in the activity and spread of the disease after the 6-month course of treatment. 133 patients with laparoscopically-diagnosed endometriosis were treated with the GnRH analogues. No

significant differences were observed between the groups in the frequency of hot flushes. The hot flushes disappeared completely from the second month on following the therapy. In the first month after the start of the medical therapy, symptoms characteristic of the menopause (colpoxerosis, nervousness, mood swings, a reduction in libido and a decrease in the size of the breasts, accompanied by hot flushes) appeared due to hypoestrogenism. As regards side-effects, no significant difference was found between the two groups. There was no significant difference between the two groups in the serum hormone levels during and after the analogue therapy. We found no significant complications with either therapy formulation. There was a noticeable decline in the symptoms of endometriosis. Dyspareunia vanished in 73% of the nafarelin group, as compared with 82% in the triptorelin group.

3.1. We examined the efficiency of HIUI following ovulation induction. This was performed, after triptorelin therapy, in patients where laparoscopically diagnosed endometriosis had elucidated the cause of their infertility and pelvic pain. At our Department, ovulation induction and HIUI were performed after GnRH analogue therapy in 33 patients with laparoscopically diagnosed endometriosis. The intervention resulted in pregnancy in 15 (45%) cases, of which 3 were twin pregnancies. In 1 case, a spontaneous abortion took place in week 15 of the pregnancy.

3.2. We sought a correlation between the female body weight and the efficiency of DIUI, with special regard to successful superovulatory treatment and ensuing pregnancies. At our Infertility Outpatient Unit, 1144 married couples attending between 1992 and 1998 asked for DIUI treatment. As a result of DIUI between 1992 and 1998, 412 pregnancies occurred, which means a success rate of 36%. Among the 412 pregnancies, there were 376 singlets, 29 twins, 6 triplets and 1 quintuplet. When the pregnancies were classified on the basis of the BMI, it could be seen clearly that DIUI can be applied most successfully in cases with a normal body weight (42%), while the pregnancy rate in overweight patients is only 21%.

In the first month of induction treatment, 5-8 (6.8 on average) ova reached a size of 20 mm in both groups. Hyperstimulation was not observed during the trial, so luteinization was performed in each case where the ovulation induction was successful. We established that there was no significant difference in pregnancy rate between the two IUI-treated groups, who had or who were free of endometriosis, but the body weight was in the normal range. After GnRH analogue treatment, ovulation induction and IUI therapy, 15 (45%) patients became pregnant as compared with ovulation induction and IUI treatment, where the success rate was 36%, but in this study the patients body weight was not ideal. When the patient's weight was

normal, the success rate was similar (42%), whereas in the low and high body weight groups the rate was lower (28-21%).

4. We suggest a treatment protocol for infertile patients who have endometriosis that calls for remove al of the endometriomas during laparoscopy, and decrease of the number of adhesions and endometrial plaques; the patients have to start ovulation induction as soon as possible, after the analogue therapy, and to supplement it with other assisted reproductive technology if required, because the success rate was significantly lower (21.8%) if we did not use ovulation induction management after the analogue therapy. We conclude that the analogue therapy and the continuous ovulation induction with monofollicular protocol and IUI represent a good therapeutic option in the management of infertility due to endometriosis. We found that 85% of the pregnancies occurred in the first two cycles.

In conclusion, we can state that nafarelin and triptorelin can be successfully applied in the treatment of endometriosis and its symptoms (dysmenorrhoea, dyspareunia and infertility). Besides having the advantage of a practical depot formulation which ensures a sustained and continuing release of the analogue, triptorelin provides a very good suppression of gonadal steroidogenesis. We found that the GnRH analogue therapy decreases the serum FSH and LH concentrations; the oestradiol levels in all patients, were initially in the postmenopausal range, were all within the normal range after the therapy. In fact, although this therapy is often referred to in the literature as "medical castration", it has been hypothesized that complete inhibition of gonadal steroidogenesis is rarely achieved with the doses of agonists in current use. In the trials, significant side-effects other than symptoms of an oestrogen deficiency (which seem to be acceptable and which promptly disappeared after the suspension of agonist therapy) were not observed either during the treatment or in the follow-up period. A cyclic pituitary-ovarian function returned within 2 months of the end of therapy. In no patient did the trial end before the set period due to side-effects or unexpected complications. The patients overcame the reversible hypoestrogenism quite well.

VI. Publications related to the thesis

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