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REVIEW

Current Place of GnRH-Analogues in The Medical Therapies of Endometriosis With Special Reference to Postoperative Treatment

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Endometriosis remains a disorder which is difficult to diagnose and to treat. It is often a progressive disease and always threatens to impair patient's fertility. It is for this reason that management is primarily dictated by the patients' hopes for permanent pain relieve and/or future pregnancies. We know the frequency of endometriosis in special groups (fig.1) but the true incidence in the female population is unknown and estimated with 8%-12% and the disease accounts for 10% to 20% of all female infertility. Although the disease has been studied for decades, the hormonal requirements or its initiation and maintenance are not fully understood. It is known that hormones secreted by the ovaries are needed for the establishment or continued presence of endometriosis because the disorder occurs only after the onset of puberty and normally disappears after menopause. Estrogen supports the growth of ectopic endometrial tissue.

Much effort in basic research has been spent for the better understanding of hormonal requirements of endometriosis as they yield clues to a treatment. A study by the National Institute of Child Health and Human Development, pregnancy research branch (1998) involved implantation of endometrial tissue in the peritoneal cavity of castrated monkey. By 12 weeks, the endometrial tissue in the control monkeys was no longer viable. The tissue in the groups receiving estradiol or progesterone or both continued to grow throughout the 16-week study.

Treatment designed to suppress ovarian function or exclude estrogen activity most likely offers the best chance for clinical remission of endometriosis ; direct regressive effects on the implants or activation of auto-antibody-reaction by medical therapy may add to atrophy. Follow-up studies have shown, that endometriosis seems to be a chronic disease with a high recurrence rate of symptoms after medical treatment and morphological examinations lead to the concept, that only permanent deprivation of estrogens can cure the disease.[1]

Because we have learned from add-back studies for the GnRH agonist treatment of uterine myoma, that the therapeutic efficacy can be reduced by ovarian steroids, the question if add-back therapy for the treatment of endometriosis should be deferred was answered by Kiesel, who presented the results of a prospective placebo controlled study (1996) with medrogestone 10 mg daily for all 6 months to the last 3 months of goserelin treatment in 123 women, which was performed in four German centres. The data demonstrates that the addition of either immediate or deferred add-back medication, such as medrogestone, does not reduce the efficacy of GnRH-analogues treatment judged by r-AFS score. The frequency and severity of hot flashes were reduced, but the bone loss was only insignificantly reduced by the progestin. Therefore, starting estrogens and progestins together with the GnRH-analogues treatment is the add-back medication of choice. These data confirm the so called estrogen threshold theory.

These facts characterize the actual situation of our knowledge about GnRH-analogues and endometriosis. There are still numerous unsolved questions in the therapeutic strategies and the lack of valid data from the literature. There is consensus in the literature, that

1. Endometriosis is a benign, proliferative, sex steroid depending disease of women, which mostly affects the reproductive organs ; it has an unclear aetiology and its pathogenesis is not yet completely understood.

2. After uterine fibroids, endometriosis is the second most common benign condition affecting women of reproductive age. Cardinal symptoms and signs are dysmenorrhea, pelvic pain, dyspareunia, urinary and defecation disorders as well as uncharacteristic abdominal and back pain appearing cyclically or acyclically.

3. Endometriosis has an association with infertility. In advanced stages, organ damage and adhesion represent mechanical causes of infertility.

4. The diagnosis must be verified by directed biopsy and histological evaluation.

5. Clinical relevance should be assessed on the basis of extent, location, type and colour of endometriotic lesions and cysts.

6. Undertreatment as well as overtreatment either with medical drugs or surgery has to be avoided.

7. Since endometriosis is often a progressive disease that continues during the reproductive age and has a high risk of recurrences periodical gynaecological follow-up including sonographic examinations are necessary.

There is still a controversy and more disagreement than agreement in the literature regarding the topic of ;

1. the currently most effective treatment for active and inactive lesions ; and

2. the indications for symptomatic, medical or surgical treatment ; and

3. the usefulness for medical treatment prior to or after surgery.

Endometriosis is characterised by a large variety of symptoms, which also occurs also in asymptomatic women. The endometriotic implants have a wide spectrum of macroscopical and microscopical appearance and they show different reactions to therapeutic attempts-whether it is a peritoneal disease, or ovarian involvement or deep infiltrating the cul de sac and the recto vaginal septum. Therefore, we need randomised placebo controlled treatment studies to get valid data about the effect of medical and/or surgical therapy, which are referring to the large variety of this disease.

Yet before this research can be done, we

need first a classification system, which takes in account not only the extent and location of the disease but also the subjective symptoms and the activity and type of implants and cysts. As scientific based data to establish such a perfect scoring system must be collected, the American Society of Reproductive Medicine proposed in December 1993 a form to standardise data collection to get more information about the relationship between endometriotic lesions and clinical signs. The analysis of these data will hopefully allow us to develop a true classification system in the future, which covers every aspect to the disease on a valid basis. Using this new scoring system in the above mentioned clinical trials for the comparison of different treatments, we will attain the information necessary for a consensus about the best individual therapeutic recommendations.

Three years ago, we started a prospective randomised trial to compare the effectivity of surgical therapy alone with surgical therapy followed by 6 months medical treatment with the GnRH agonist as depot preparation. Pain Score and AFS Score were used to classify the symptoms and the extend of the disease. Macroscopical and microscopical criteria were used to classify the implants in active and inactive endometriosis. At the interim evaluation (fig. 11 and fig. 12) of the study Dec. 1996, 379 patients were recruited. The endometriosis was differentiated in active and inactive disease using macroscopic (fig. 13) and microscopic (fig. 14) criteria.

In patients treated for endometriosis related symptoms-mainly pain-the recurrence rate and the

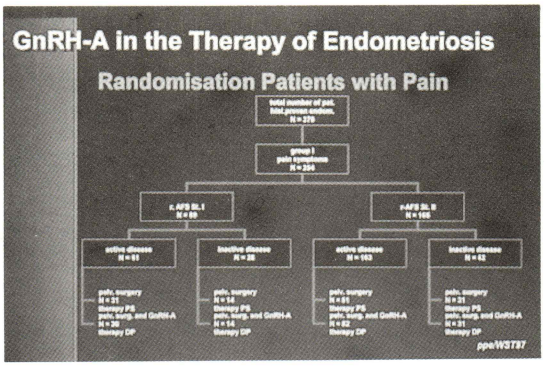

Fig. 11.

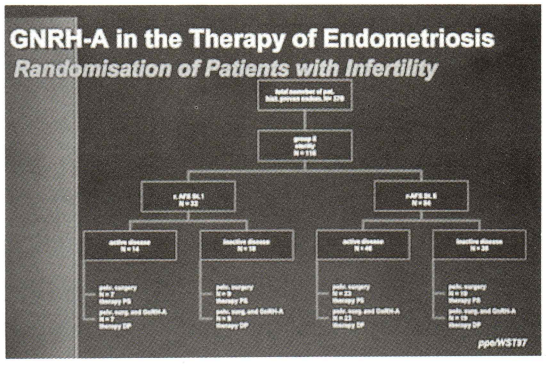

Fig. 12.

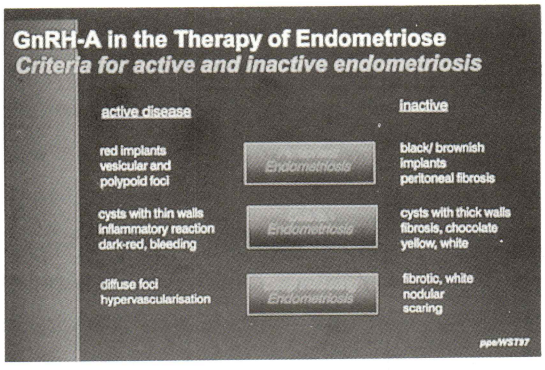

Fig. 13.

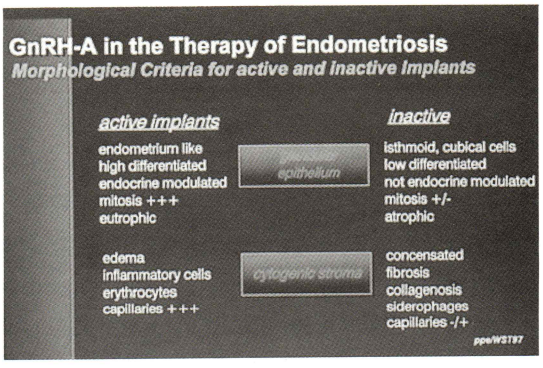

Fig. 14.

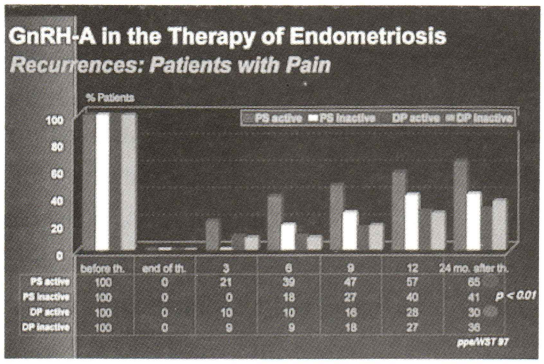

Fig. 15.

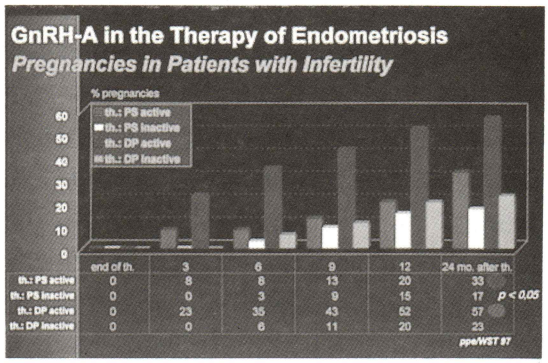

Fig. 16.

recurrence free interval were judged as endpoints of the study. In infertile patient, the pregnancy rate was the criterium for the effectiveness of treatment.

In case of active disease the recurrence rates and the recurrence free intervals were significantly improved using a GnRH agonist treatment postoperatively. Patients with inactive endometriosis had no benefit from a postsurgical medication (fig. 15).

In the group of infertile patients with active endometriosis the medical therapy for 6 months using a GnRH agonist leads to a significant higher pregnancy rate and an earlier achievement of pregnancy when compared to pelviscopic surgery alone. No significant differences were found in patients with inactive endometriosis and infertility between the examined treatment schedules. (fig. 16).

From these preliminary data were draw the conclusion :

1. in case of active endometriosis pelviscopic surgery alone is insufficient (because microscopic disease is overlooked) and medical treatment after surgery will improve the recurrence free intervals and reduce the recurrence rates in symptomatic patients and will improve the pregnancy rates in infertile patients.

2. in case of inactive endometriosis surgery alone is best for symptomatic patients and in case of infertility inactive disease is probably not a cause of reduced fertility ; no medical therapy is indicated.

Management Strategies in the Treat ment of Endometriosis

A summary of our current therapeutic strategies is given. In order to arrive at practicable decisions, endometriosis patients are categorised with respect to their families being completed or not and whether they present for complaints or for infertility.

The group of patients clinically suspect of endometriosis and not desiring further more pregnancy has an average age of 35 years. In stage I and II the diagnostic laparoscopy can be extended to thermocoagulation, vaporisation, ultracison and adhesiolysis and resection of implants and residual fibrosis. Thereafter, follow-up is directed to recurrence, which then would ask for an additional hormonal regimen-that is postsurgical medical treatment with delay. In stages II and III, a 3 to 6 months medication of a GnRH-analogues preferable depot preparation-should follow endoscopic surgery if histological examination shows an active disease. In stage IV

the procedure for women under 45 years is identical to stage III. Patients older than 45 years with evident recurrence are subject to definitive surgery ; abdominal hysterectomy and bilateral salpingo-oophorectomy would be the method of choice.

The question remains, whether preoperative use of a hormonal regimen such as leuprorelin would be beneficial. Besides the already mentioned advantages with respect to reduction in extent of surgery and adhesions, reduced vascularity and less inflammation of pelvic organs noted at the time of revaluation may also be helpful in preventing the development of postoperative adhesions. In fact, in some cases, filmy adhesions noted at initial laparoscopy were not visible at revaluation. The reason for this is unclear.

When clinical complaints are evident and fertility is not an immediate issue, minor endometriosis visible at diagnostic laparoscopy should be thermocoagulated. In stages II and III the patient should primarily be subjected to a hormonal regimen if the endometriosis can be characterised as active by macroscopic and microscopic criteria. In severe cases the efficiency of which can be controlled by repeat laparoscopy right after completion of the hormonal regimen, because one third had persistent disease, as mentioned earlier. The pelviscopic control would then include thermocoagulation and adhesiolysis or be extended to microsurgery, just depending on the individual experience of the surgeon and the endoscopic equipment of the hospital. At stage IV primary microsurgical reconstruction is to be preferred. In the case of incomplete resection 3 to 6 months of GnRH agonist should follow the surgery to inactivate residual and microscopical implants. The chance for pregnancy is best in the first 12-18 months following this procedure.

Finally, there is the young infertile women with no clinical evidence of endometriosis, who in their follow up are found to have endoscopic and histological evidence of endometriosis. This woman would also be primarily subject to pelviscopic treatment using thermocoagulation, bipolar coagulation or vaporisation followed by a 6-12 months interval, eventually accompanied by the induction of ovulatory cycles. Should there be no conception, here a delayed postoperative hormonal regimen is best indicated as secondary suppressive therapy. Following another 6 to 12 months interval, repeat pelviscopy is mandatory including endoscopic surgery if necessary. Stage II and III endometriosis, according to our above mentioned strategies, should be subjected to a primary hormonal regimen, especially if the implants are highly differentiated and endocrine modulated judged by histological criteria, and active judged by macroscopic criteria. Further advanced stages are subject to primary microsurgery, which in these cases proves to be extremely successful. In severe cases with cystic ovarian involvement a preoperative medical treatment with GnRH-analogues for three months is reasonable.

Summary

In conclusion : the development of GnRH-analogues offers a therapeutic principle, which is effective in relief of symptoms and regression of endometriotic implants. The profile and frequency of side effects may be the most important difference in comparison to the standard regimens of the past. The reasons why some women are prone to develop endometriosis are not understood, but the patients hormone milieu is probably important. The common association of endome- triosis with infertility is explained, in part, by the fact that many of these patients do

not ovulate regularly and in progressed disease by mechanical disturbances of ovarian and tubal function.

Treatment is dictated by the severity of symptoms and signs primarily, but also and very important for the patients' hope of future pregnancies. If patient's family is complete, then management is easier and will often favour a surgical cure followed by postoperative medication in case of residual disease or recurrence of symptoms.

Large tumours or less differentiated endometriomas or inactive nodular implants do not respond to hormone therapy and indicate the need for a surgical intervention. In mild to moderate disease, medical treatment may be effective postoperatively especially if there are mixed forms and in addition active implants, but such patients who are planning a pregnancy should first be encouraged to start their pregnancy without delay. Alternatively, they would mostly be subjected to GnRH-analogues treatment. In patients complaining of infertility, additional drugs to stimulate ovulation may be required and in extensive disease with mechanical disturbances of the reproductive organs. IVF-ET is the treatment of choice after a course of GnRH agonists to inactivate the endometriosis (so called long protocol).

The wide differences in patients expectation, in pathological findings severity of the disease, in morphological differentiations and biochemical characteristics, in reaction of the endometriotic implants and cysts to medical treatment make an individualised therapeutic regimen necessary. Following hormonal therapy, recurrent endometriosis and progressed stages are common experience. This is the domain of endoscopic operations and microsurgery. Medical treatment before and/or surgery obviously adds to the therapeutic success. Definitive surgery does not require follow-up medication.

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