Goserelin versus danazol in the treatment of endometriosis

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Summary: Fourteen patients affected by endometriosis were treated by Danazol (7) and by Goserelin (7). The two treatments were compared. From the study it emerged that both treatments were equally effective; however, the analogs gave a more favourable therapeutic profile.

As is well known endometriosis is one of the most widespread gynecological diseases. The etiopathogenesis is still obscure and, in fact, the various assumptions made up to now have not cleared the picture (1).

Hypotheses have been formulated on the spreading of endometrial tissue by hematic or lymphatic routes, or on the reflux of endometrial tissue through the tubes. Other assumptions centre upon familiar, auto-immune, dysgenic causes, upon an anomalous differentiation of some residual cells from the müllerian epithelium or, finally, upon metaplasia of the celomatic germinal epithelium.

This vast range of hypotheses has generated several therapeutic solutions which, leaving out a surgical approach, can be summed up in two groups:

1) induction of a pharmacological pseudopregnancy (2) through the prolonged and continued use of estrogens and progestagens, so as to turn the islands of ectopic endometrial tissue into decidualized cells combined with a few inactive glands;

2) induction of a pharmacological pseudomenopause, through suppression of the secretion of hypophysial gonadotropins, which provoke a condition of hypoestrogenism sufficient to determine atrophy of the endometrium.

The drugs which induce a condition of pseudo-menopause can be divided into two groups: one including androgen derivatives such as danazol (3) and gestrinone (4), and another which groups together the GnRH hyperactive agonists.

The isolation and comprehension of the structure of GnRH in 1971 has made it possible to produce hundreds of peptides associated with it, whose biological potential is 20-200 times higher than the natural molecule's. The increase in the biological activity is strictly related to the rise in the resistance to proteolitic enzymes and with a greater affinity for GnRH hypophysial receptors, through modification of the natural molecule.

One of the analogues most used in the treatment of endometriosis is busere-

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lin ([7]), which must be administered many times daily. Another widely employed analogue is goserelin, which, has recently been rendered available in depot, and which can thus be given by means of monthly subcutaneous injections.

Our research aims at an evaluation of the metabolic, endocrine and clinical effects of depot goserelin and of danazol upon patients suffering from endometriosis and treated during a period of nine months.

MATERIALS AND METHODS

Fourteen women in ages ranging from 24 to 40 years affected by symptomatic endometriosis diagnosed through laparoscopy or after laparotomy through pelvic surgery were admitted to the study. Pelvic endometriosis was studied according to the American Fertility Society classification. Depot goserelin (3.6 mg) was administered subcutaneously to seven patients every four weeks in the front abdominal paries. The other seven patients were administered orally 600/800 mg die. For all patients the treatment lasted nine months, and the first administration coincided in all cases with the beginning of a menstrual cycle. Clinical, endocrine and metabolic assays were performed at the beginning of the treatment, two weeks later, three months later and, afterwards, every three months in a period of a year from the beginning of the therapy. We considered in detail body weight, headaches, hot flushes, acne, muscular cramps, dejection, sudation. The treatment was monitored through control of estradiol, and of luteinizing and follicle-stimulating hormones. Hepatic enzymes (ALAT, ASAT, gamma GT), total and fractional bilirubin, prothrombin, fibrinogen (Factor I), total and HDL cholesterol, glycemia were also checked. Moreover, each patient underwent control of the distal radius' bone density by means of a dual photon absorptionometry (Osteoden / P: I^{125}, AM^{241}).

ACHIEVEMENTS

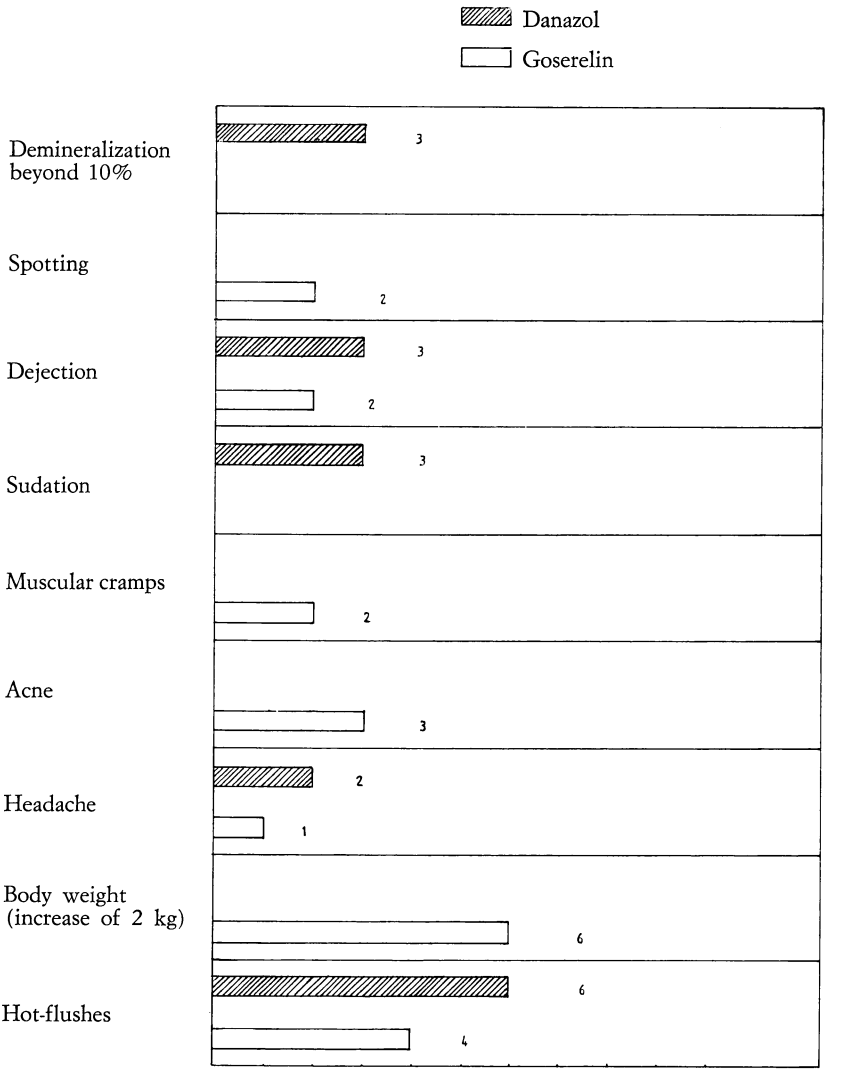
In ten patients the range of pelvic endometriosis was II, in three of them it was III, and in one it was IV. All patients completed the nine-month treatment. In most cases they became amenorrheic by the second month (five after the first cycle, seven after the second; two patients who had initially been included in the "danazol" group were moved to the "goserelin" one because of continued or intermittent spotting, despite the relatively high dosage of 800 mg). Obviously the specific symptoms of the disease were reduced in all patients. In six patients out of seven, among those who were given danazol, body weight increased. Headache was attested in two cases in the "goserelin" group and in one case only in the "danazol" one. Hot flushes occurred both in the group which was using goserelin (six cases) and in that which was using danazol (four cases), though, indeed, with decreasing intensity.

Acne appeared in only three patients who were being administered danazol, and so did muscular cramps (two cases). Sudation, especially nightly (three cases), and dejection were observed in patients who were using goserelin (see table 1). Gonadotropins and estradiol assay were useful in performing hormonal monitoring.

LH and E_2 rapidly decreased to non-dosable ranges, while FSH proved to be fluctuating both in patients treated with goserelin and in those who were being administered danazol. In both groups hematic ranges were normal. No important variations of HDL cholesterol were observed in the goserelin group, whereas in the one using danazol increase in LDL and decrease in HDL were noticed.

Finally, as to the radius' bone density (10th distal of the non-dominating lemb), we observed a progressive worsening in the patients who were using goserelin (in three cases the diminution was beyond 10%, in the others the drop was lower), while in the patients administered danazol no considerable variations were noticed.

Table 1. – *Incidence of side effects in the patients treated with Goserelin or with Danazol.*



DISCUSSION

Our research corroborates many observations on the therapeutical efficacy of GnRH and danazol in the treatment of endometriosis. Generally speaking, the two kinds of treatment are well tolerated ([9]).

Treatment with goserelin provoked, indeed, only slight side effects such as hot flushes ([10]) or a reduction of bone density as had already been noticed by Steingolds and other Authors ([11]), while we did not observe any alteration of lipid metabolism. On the contrary, we noticed in the

treatment dosage 600/800 die with danazol the appearance of side effects such as acne and muscular cramps; no hepatic distress was noticed. We observed, moreover, interaction with lipid metabolism, and no remarkable effects on bone density.

Our observations agree with those formulated by other Authors ([12, 13]) who, though maintaining that GnRH agonist analogues and danazol have the same efficacy in the treatment of endometriosis, report that the analogues have a more favourable therapeutical action ([14]). The most serious effect of the analogue-therapies, that is, reduction in bone mass, has also been considerably reduced ([12]); on the contrary, it is now well known that it is dose-related ([15]) and that it is even reversible once the treatment is interrupted. As to this aspect, a very interesting suggestion is that of adding small quantities of progestinics to the GnRH agonist therapy so as to successfully prevent temporary demineralization too.

CONCLUSION

The recent use of drugs which induce a pseudo-menopause has sensibly improved the therapy of endometriosis. Danazol and GnRH analogue agonists achieve, though in different ways and separately, results which were considered impossible to attain up to a few years ago. The research carried out up to now hase helped to point out the differences between the two types of treatment and, indeed, suggesting the consideration of danazol (on the one hand) and the GnRH agonists (on the other) as complementary, or at least not in antithesis, is more and more credited. It will be helpful to consider the treatment with analogues when patients are affected by dyslipidaemiae, obesity, vasculopathies, hepatopathies; the use of danazol is, on the other hand, advisable in cases which present evident risks of osteoporosis (relative body mass-index below 80%, diets poor in calcium, sedentary life, etc.).

REFERENCES

1) Benagiano G., Napolitano C., Marziani R.: "Endometriosis: past, present and future". In: "Progress in Gynecology and Obstetrics". Eds A. A. Genazzani, Petraglia F., Volpe A. Parthenon Publ. Group, Madonna di Campiglio, 1989.
2) Kistner R. W.: "The use of newer progestins in the treatment of endometriosis". *Am. J. Obst. Gyn., 75*, 264, 1958.
3) Greenblatt R. B., Dnowski L. P., Mahesh U., Scholer H. F. C.: "Clinical studies with an antigonadotrophin-danazol". *Fertil. Steril., 22*, 102, 1971.
4) Coutinho E. M.: "Treatment of endometriosis with gestrinone (R2323) a synthethic antiestrogen, antiprogesterone". *Am. J. Obst. Gyn., 144*, 895, 1982.
5) Schally A. V., Arimur A., Kastin A. J.: "Gonadotrophin-releasing hormone: polypeptide regulates secretion of luteinising and follicle-stimulating hormone". *Science, 173*, 1036, 1971.
6) Loumaye E., Naor Z., Catt K. J.: "Binding affinity and biological activity of gonadotrophin-releasing hormone agonists in isolated pituitary cells". *Endocrinology, 111*, 730, 1982.
7) Lemay A., Maheux R., Faure N., Jean C., Fazekas A.T.A.: "Reversible hypogonadism induced by a luteinizing hormone-releasing hormone (LH-RH) agonist (Buserelin) as a new therapeutic approach for endometriosis". *Fertil. Steril., 41,* 863, 184.
8) The American Fertility Society: "Revised American Fertility Society classification of endometriosis". *Fertil. Steril., 43,* 351, 1985.
9) Massobrio M., Trossarello G. F., Ardizzoia M., Guidetti D.: "Trattamento ormonale dell'endometriosi". *Perspect. Gyn. Obst., 4, 55*, 1987.
10) Mais V., Melis G. B., Paoletti A. M., Gambacciani M., Spinetti A., Petacchi F. D., Mauro G. A., Fioretti P.: "Endometriosis therapy with Zoladex". In: "Progress in Gynecology and Obstetrics". Eds. Genazzani A. R., Petraglia F., Volpe A., Madonna di Campiglio, Parthenon Publ. Group, 1989.
11) Steingold K. A., Cedars M., Lu J. K. H., Roundle D., Judd H. L., Meldrum D. R.: "Treatment of endometriosis with a long

acting gonadotrophin-releasing hormone agonist". *Obst. Gyn., 69,* 403, 1987.

12) Henzl M. R., Kwei L.: "Efficacy and safety of naferelin in the treatment of endometriosis". *Am. J. Obst. Gyn., 162,* 570, 1990.

13) Rolland R., Van der Heijden P. F. M.: "Nafarelin versus danazol in the treatment of endometriosis". *Am. J. Ost. Gyn., 162,* 586, 1990.

14) Bergquist C.: "Effects of nafarelin versus danazol on lipids and calcium metabolism". *Am. J. Obst. Gyn., 162,* 589, 1990.

15) Jacobson J. B.: "Effects of nafarelin on bone density". *Am. J. Obst. Gyn., 162,* 591, 1990.

16) Barbieri R. L.: "Gonadotropin-releasing hormone agonists and estrogen-progestogen replacement therapy". *Am. J. Obst. Gyn., 162,* 595, 1990.

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