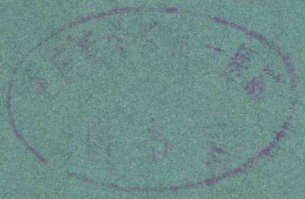
Advances in Diagn

and

Treatment of Infertility

Editors
Vaclav Insler
and
Gerhard Bettendorf



ADVANCES IN DIAGNOSIS

AND

TREATMENT OF INFERTILITY

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VACLAV INSLER and GERHARD BETTENDORF

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Symposium Held in Bad Reichenhall, West Germany
June 30–July 3, 1980

Sponsored by ORGANON

ELSEVIER/NORTH-HOLLAND
New York • Amsterdam • Oxford

Elsevier North Holland, Inc.
52 Vanderbilt Avenue, New York, New York 10017

Sole distributors outside USA and Canada:
Elsevier Science Publishers B.V.
P.O. Box 211, 1000 AE Amsterdam, The Netherlands

Library of Congress Cataloging in Publication Data

Main entry under title:

Advances in diagnosis and treatment of infertility.

Bibliography: p.
Includes index.
1. Sterility—Congresses. I. Insler, Vaclav. II. Bettendorf, Gerhard. [DNLM: 1. Sterility—Diagnosis—Congresses. 2. Sterility—Therapy—Congresses. WP 570 A244 1980]
RC889.A38 616.6'92 80-28242
ISBN 0-444-00584-6

Editorial Services Barbara Conover
Design Edmée Froment
Design Editor Virginia Kudlak
Cover Design Paul Agule Design
Production Manager Joanne Jay
Compositor The Composing Room of Michigan, Inc.
Printer Haddon Craftsmen

Manufactured in the United States of America

FOREWORD

The ORGANON symposia have become a tradition. They have always focused on reproductive medicine, and we were glad to have had the opportunity to participate in the organization of three of these events. The infertility symposium, however, differed from the previous ones because it had a broader scope. While the previous symposia dealt in depth with specific aspects of reproduction, the infertility symposium attempted to bring into focus the spectrum of human fertility problems. The papers presented and discussed, as well as the informal talks, stressed the necessity of a team approach.

Infertility is a complex process involving medical, psychological, and social aspects in women and men. The medical profession's obligation toward infertile couples will be fulfilled only when all these aspects are considered. This has to be accomplished by a joint effort of various specialists united in one medical discipline: reproductive medicine. It is our hope that this symposium will contribute to the realization of this goal.

We would like to express our appreciation to ORGANON and particularly to Dr. Günter Weiland for sponsoring and organizing this meeting. Thanks are also owed to all those who participated in and contributed to the scientific program. We are grateful to Mr. Yale Altman of Elsevier North Holland, Inc., New York, for his cooperation.

Vaclav Insler
Gerhard Bettendorf

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GONADOTROPIN-RELEASING HORMONE AND ITS AGONISTS FOR INDUCTION OF FOLLICULAR MATURATION AND OVULATION

S. J. NILLIUS, G. SKARIN, AND L. WIDE

The hypothalamic gonadotropin-releasing hormone was isolated, structurally determined, and synthesized by Schally and his co-workers in 1971. Luteinizing hormone-releasing hormone (LRH) was found to stimulate the pituitary synthesis and release of not only luteinizing hormone (LH) but also follicle-stimulating hormone (FSH) (Schally et al., 1971). Initial studies with natural and synthetic LRH suggested that the hormone should find practical clinical applications (Schally et al., 1971, 1972). It was hoped that LRH would prove particularly useful for diagnosis and treatment of infertility.

Because synthetic LHR preparations became available the potential diagnostic and therapeutic use of gonadotropin releasing hormone has been explored extensively. To enhance and simplify treatment, superactive analogs of LRH with prolonged biological activity have been synthesized (Schally et al., 1976). It is generally agreed that LRH is of limited value in diagnostic evaluation of female infertility. Single determinations of FSH and prolactin in serum and the exogenous progesterone are the only distinguishable investigative tools for selection of anovulatory women for treatment with ovulation-inducing agents (Bergh et al., 1978). Clinical trials with LRH were performed over several years before an effective therapeutic regimen was established. Chronic intermittent treatment (subcutaneous injections of 500 μg of LRH every 8 hours) proved to be effective in inducing potency and spermatogenesis in hypogonadal men (Mortimer et al., 1974) and follicular maturation and ovulation in women with amenorrhea (Nillius et al., 1975).

In the female, the most relevant indication for LRH therapy is induction of follicular maturation and ovulation in those amenorrheic women who at present have to be treated with human gonadotropins. LRH might also be used for timing of ovulation in normally menstruating women in association with artificial insemination, and for induction of ovulation in anovulatory women, in whom follicular maturation has been elicited by clomiphene citrate or human

Supported by grant 13x - 3145 from the Swedish Medical Research Council.

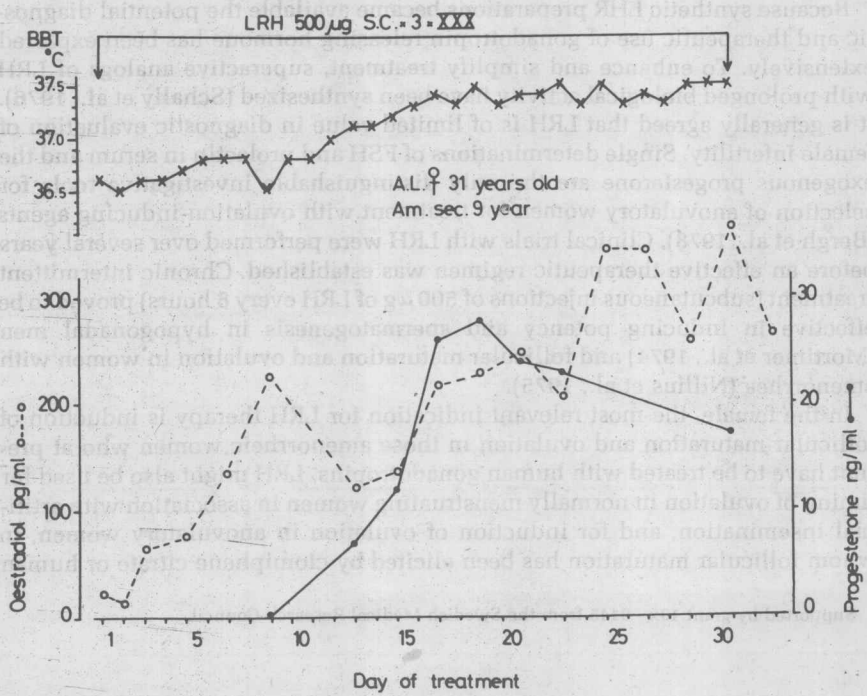
V. Insler and G. Bettendorf, eds. Advances in Diagnosis and Treatment of Infertility.

menopausal gonadotropins (hMG). For discussions of these indications the reader is referred to previous reviews on the therapeutic use of LRH in the human female (Nillius 1976, 1979; Nillius et al., 1978). This chapter reviews the therapeutic use of LRH and one of its new potent agonists in amenorrheic infertile women.

CHRONIC INTERMITTENT LRH TREATMENT

The therapeutic regimen with self-administration of LRH subcutaneously every 8 hours proved to be effective in clomiphene-resistant amenorrheic women with no signs of endogenous estrogen production (Mortimer et al., 1975; Nillius et al., 1975; Nillius and Wide, 1975; Henderson et al., 1976). By prolonged treatment with LRH only, it was possible to induce follicular growth and maturation, ovulation, and corpus luteum formation in amenorrheic women who had been practically devoid of ovarian activity before the treatment. Figure 1 shows an LRH treatment resulting in pregnancy in an estrogen-deficient woman who had experienced amenorrhea for 9 years. She had previously had a child after treatment with human gonadotropins and monitoring by daily estrogen determinations. During the LRH treatment she self-administered the

FIGURE 1. Chronic intermittent treatment with 500 μg of LRH subcutaneously every 8 hours in a woman with long-standing amenorrhea. Basal body temperature and serum levels of estradiol and progesterone during a treatment resulting in pregnancy. Reproduced from Nillius, 1979.



hormone at home and after 30 days of treatment returned pregnant without any symptoms or signs of ovarian hyperstimulation.

Chronic intermittent administration of a constant dose of the single gonadotropin-releasing hormone had not only normalized basal FSH and LH secretion but also induced a cyclic gonadotropin pattern with differential changes of LH and FSH responses to LRH during the treatment (Nillius and Wide, 1979). The maximal FSH levels were obtained during the first days of treatment. However, the FSH levels rapidly decreased during the treatment and this decrease became more marked when the estrogen secretion from the ovaries started to rise. The LH responses, on the other hand, progressively increased during the treatment and in most patients reached maximal midcycle peak levels concomitant with high estrogen levels consistent with full follicular maturation.

The striking changes in the gonadotropin responses to LRH during the prolonged treatment may give LRH therapy an advantage over hMG for induction of follicular growth and maturation. The feedback system between the ovaries and the pituitary is intact in patients treated with LRH. This internal control mechanism may automatically prevent excessive FSH stimulation of the ovaries during prolonged treatment with LRH. The FSH response to LRH decreases when the estrogen levels rise concomitant with follicular maturation.

Fourteen amenorrheic women with no signs of endogenous estrogen production were given chronic intermittent therapy with 500 μg of LRH every 8 h for 28 days. Follicular maturation and ovulation were induced in 11 women. Two of the five women, who were treated for anovulatory infertility, became pregnant during the treatment course. However, low progesterone values during the premenstrual period suggested insufficient corpus luteum function in no less than 6 of 12 treatment cycles. In an attempt to improve luteal function, LRH was then given in combination with human chorionic gonadotropin.

Combined treatment with LRH and hCG was given during five treatment courses (Nillius and Wide, 1979). The treatment was monitored by daily estrogen determinations for optimal timing of hCG injection and one of the three infertile patients conceived. This patient was later delivered of a second child after combined LRH–hCG treatment.

Thus, in some anovulatory women it is possible to replace human gonadotropins by LRH. Amenorrheic patients with relatively high FSH responses to LRH seem to be particularly suitable for LRH therapy, but absence of pretreatment response to LRH does not preclude successful treatment with daily applications of LRH alone, although insufficient corpus luteum function often occurs. For effective treatment of anovulatory infertility, it is therefore necessary to combine LRH and hCG in order to secure normal ovulation and adequate corpus luteum function. This treatment has to be monitored by daily estrogen determinations. One of the big advantages of LRH therapy is then lost.

CHRONIC LRH AGONIST TREATMENT

During the last few years stimulatory analogs of LRH have become available for clinical trials. One of the most potent LRH agonists is D-Ser (TBU)^{6}-EA^{10}-LRH (Sandow et al., 1978). The effect of this LRH analog on the gonadotropin and

gonadal steroids secretion was studied in 10 women with amenorrhea (Nillius and Wide, 1977). A comparison was made between the acute effects of a subcutaneous injection of 500 μg of LRH and 10 μg of LRH and 10 μg of D-Ser (TBU) ^{6}-EH ^{10}-LRH. The FSH and LH release during the first 3 h was similar but the gonadotropin release during the remainder of the study period was greater after administration of the analog and so was the estradiol increase. Thus, the LRH agonist was shown to exhibit a more potent and prolonged effect on the gonadotropin secretion than did LRH.

Chronic treatment with daily subcutaneous injections of 10 μg of LRH agonist was then instituted in seven amenorrheic women with no evidence of endogenous estrogen secretion (Skarin et al., 1980). The acute effect of the LRH agonist in these women is shown in Figure 2. There was an evident biphasic pattern of LH release with early and late peaks of LH combined with a gradual progressive FSH release. This pattern is similar to that described after extended pituitary stimulation by constant infusions of LRH. All women responded with

FIGURE 2. Acute effects of a potent LRH agonist on the serum LH, FSH, and estradiol levels in seven women with amenorrhea. Reproduced from Skarin et al., 1980.