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Autor: Staemmler, H.-J. / Jung, K.

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Clinic of Obstetrics and Gynecology, Ludwigshafen/Rhein

Induction of Ovulation with Sexual Steroids

H.-J. Staemmler and K. Jung

Ovulation can be induced with human gonadotropins, sexual steroids and clomiphene in cases of ovarian dysfunction.

To carry out the therapy with gonadotropins it is essential that the ovary can be stimulated. On the other side, a sufficient endogenous production of gonadotropins is necessary to give a positive response to sexual steroids and clomiphene.

The effect of high doses of sexual steroids has generally to be explained by the rebound effect, the response to low doses by the Hohlweg- or the Collip-effect.

These conclusions are based on animal experiments mainly. In humans they can only be shown with difficulties. The importance of psychic factors cannot be overlooked in normal clinical experiments. Patients whose ovulation is induced by low doses of estrogens and gestagens above all show a special lability of their ovarian function. Therefore, an exact evaluation of clinical results is only possible by double-blind experiments. Our experiences are based on the trial with clomiphene.

Material and method

Patients and treatment: On 41 patients, aged 18–39 years, we have used the retrosteroid Ro 4-8347 which is similar to dydrogesterone. On the whole, 95 treatments have been carried out from the 5th to 14th day after the beginning of uterine bleeding. In amenorrhoic patients, bleeding was induced by treatment with estrogen-gestagen combinations. With a few exceptions the dosage was 4 mg/day.

Selection: Amenorrhoic patients who showed hypoplastic ovaries on examination by coelioscopy, laparotomy, or analysis of the gonadotropins were not included. Furthermore, all patients with dysfunction of the suprarenal gland or of the thyroid gland (analysis of C_{17}-ketosteroids and 17-hydroxysteroids, ACTH test, radioiodide test) were excluded.

Controlling measures: All patients had to take their basal body temperature (cyclotest thermometer) rectally. If corpus luteal insufficiency was suspected, a diagnostic abrasion was made at the beginning of uterine bleeding. Repeated tests of the karyopyknose index in vaginal smears were only made on patients with amenorrhea for several years. The same can be said of the repeated control of the gonadotropins (immunological method done in our own laboratory, biological method done in the

Table I

Secondary amenorrhea

Duration of amenorrhea (years)	Number of patients	Number of treatments	No bleeding	Spotting (monophasic)	Breakdown bleeding (monoph.)	Biphasic reaction
½–1	7	16	5	1	9	1
>2–6	3	9	4	0	3	2
>6–13	6	12	6	2	3	1
Total	16	37	15	3	15	4

Neuroendocrinological Laboratory at Landeck, Dr. LASCHET). Special conclusions could not be drawn from these analyses because of the small number of cases.

Results

A. Secondary amenorrhea (Table I)

16 patients aged between 18 and 38 years have undergone 37 treatments for 10 days. Indications of ovulation (biphasic basal body temperature, secretory endometrium) resulted in 4 treatments only. Anovulatory bleedings were seen 3–13 days (on the average 5 days) after the last day of treatment. 7 patients were treated with clomiphene, HMG-HCG or an epiestriol derivate (5 mg/day for 10 days) before or after treatment with Ro 4-8347.

I. E., 38 years, amenorrhea for 13 years. Clomiphene: no reaction. Ro 4-8347 no reaction. HMG-HCG (2 treatments): conception; at the moment grav. mens. IX.

Th. R., 31 years, amenorrhea for 9 years. Clomiphene (2 treatments): no reaction. Ro 4-8347 (2 treatments): no reaction. HMG-HCG: conception,, partus praematurus on 3. 9. 69, female, 1730, 43 cm.

M. K., 30 years, amenorrhea for 7 years. Clomiphene (2 treatments): biphasic basal body temperature. Ro 4-8347: anovulatory bleeding 3 days after the end of the treatment. HMG-HCG: conception. Delivery on 12. 4. 68. Triplets. Infants are well.

S. K., 20 years, amenorrhea for 6 months. Ro 4-8347: no effect. Clomiphene: biphasic basal body temperature. Epiestriol: anovulatory bleeding.

G. Sp., 18 years, amenorrhea for one year. Ro 4-8347 (4 treatments): 2 monophasic bleedings. Epiestriol (3 treatment): no effect.

E. B., 20 years, amenorrhea for 3 years. Gonadotropine excretion < 1.5 IE $= <6$ MUE/day. Total urinary estrogens: 18.9 and 21.0 µg/day. Ro 4-8347 (4 treatments): no reaction. Epiestrol: no reaction.

J. Sch., 19 years, amenorrhea for 6 months, slight hirsutism (C_{17}-ketosteroids: 12.6 mg/day; PJ: 40%). Ro 4-8347 (2 treatments): anovulatory breakdown bleeding. Epiestriol: bleeding 51 days after the end of the medication.

B. Primary functional sterility (Table II)

We examined 15 patients aged 24–37 years. Having examined the husbands, done a post-oital test, a hysterosalpingography and control of the basal body temperature for several months, we felt the causes of sterility had to be regarded as due to anovulatory cycles or corpus luteum insufficiency.

Table II

Primary functional sterility

	Number of		No bleeding	Spotting[1]	Breakdown bleeding[1]	Biphasic reaction	Conception	
	patients	treatments					at the same cycle	later
Mono- and biphasic oligomenorrhea[2]	9	24	1	3	11	8	1	3
Corpus luteum insufficiency	6	15	0	0	2	13	0	1
Total	15	39	1	3	13	21	1	4

[1] monophasic

[2] partly with intercurrent amenorrhea

On the whole 39 treatments over 10 days were carried out. The monophasic breakdown bleeding occurred 2–10 days after the end of the treatment (on an average on the 6th day). In cases of biphasic basal body temperature the lowest degree could be noted from the 2nd to the 14th day after the end of the treatment, in 1 case on the 5th and in another one the 9th day after the beginning of therapy. 5 of the 15 women became pregnant. One patient had an early abortion. Only one became pregnant during the Ro 4-8347 -induced cycle(M. D., 29 years, delivery on 21. 8. 69, ♂, 4050 g, 55 cm).

8 patients were treated with clomiphene, epiestriol, of HMG-HCG before or after treatment with Ro 4-8347.

R. B., 32 years, monophasic oligomenorrhea. Clomiphene (3 treatments): biphasic reaction. Ro 4-8347 (2 treatments): monophasic reaction.

R. K., 27 years, monophasic oligomenorrhea (with intercurrent amenorrhea). Clomiphene (2 treatments): monophasic reaction. HMG-HCG: highly overshooting reaction. Pregnanediol: 32.4 mg/day. The punctate from the Douglas' pouch contained 28.1 mg progesterone/100 ml.

J. L., 24 years, monophasic oligomenorrhea. Ro 4-8347 (4 treatments): biphasic reaction with cystic reaction of the ovaries. On May 22nd 1968 laparotomy, bilateral ovarian cystectomy: Stein-Leventhal syndrome. Epiestriol: monophasic reaction. HMG-HCG: milder cystic reaction of the ovaries.

D. L., 28 years, mono- and biphasic oligomenorrhea. Clomiphene (2 treatments): biphasic reaction. Ro 4-8347 (5 treatments): 2 biphasic, 3 monophasic reactions. HMG-HCG: biphasic reaction, no signs of overstimulation.

H. N., 38 years, monophasic oligomenorrhea. Clomiphene (3 treatments): biphasic reaction. Ro 4-8347 (2 treatments): monophasic reaction. HMG-HCG: biphasic reaction.

E. F., 30 years, corpus luteum insufficiency. Clomiphene (3 treatments): biphasic reaction with slight overstimulation. Ro 4-8347 (2 treatments): monophasic reaction

Table III

Secondary functional sterility

	Number of		No bleeding	Spotting[1]	Breakdown bleeding[1]	Biphasic reaction	Conception	
	patients	treatments					at the same cycle	later
Mono and biphasic oligomenorrhea[2]	5	8	0	0	4	4	2	0
Corpus luteum insufficiency	5	11	0	0	0	11	1	1
Total	10	19	0	0	4	15	3	1

[1] monophasic

[2] partly with intercurrent amenorrhea

M. F., 25 years, corpus luteum insufficiency (hirsutism, quite enlarged ovaries). Ro 4-8347 (2 treatments): biphasic reaction, but still corpus luteum insufficiency. Epiestriol: conception!

H. W., 36 years, corpus luteum insufficiency. Clomiphene (2 treatments): monophasic reaction! Ro 4-8347 (3 treatments): normal corpus luteum phase.

C. Secondary functional sterility (Table III)

10 patients aged 20–39 years were treated. For this group the same conditions were used as for the patients with primary sterility. The monophasic breakdown bleedings began in the first week after the end of the treatment.

The probable day of ovulation (indicated by the lowest point of the basal body temperature curve) varied between 4 and 8 days after the end of the treatment. 4 of the 10 patients became pregnant. One patient had an early abortion. One woman was delivered of a male baby (3350 g, 51 cm) on 3. 1. 69.

We compared this group of patients with another treated by other methods:

V. B., 30 years, monophasic oligomenorrhea. Ro 4-8347: biphasic reaction. Clomiphene: biphasic reaction; 5 months later conception, up to now no disturbances of the pregnancy.

J. K., 32 years, anovulatory cycles, slight hirsutism. Quite enlarged ovaries (Stein-Leventhal syndrome?). Clomiphene (4 treatments): each time biphasic reaction. Ro 4-8347 (2 treatments): one monophasic reaction, after the second treatment ovulation and conception, early abortion.

Ch. M., 30 years, mostly anovulatory cycles. Ro 4-8347 (2 treatments): one biphasic and one monophasic reaction. Clomiphene (50 mg/day): conception during the same cycle. Up to now no disturbances of the pregnancy.

R. K., 34 years, corpus luteum insufficiency. Clomiphene (2 treatments): biphasic reaction with normal corpus luteum phases. Epiestriol: biphasic reaction, but shortened corpus luteum phase. Ro 4-8347 (3 treatments): biphasic reaction with normal corpus luteum phase.

Discussion and Conclusions

The experiences with the progestational retrosteroid Ro 4-8347 were made on 41 patients suffering from a more or less pronounced ovarian insufficiency. The 95 treatments were carried out over 10 days. As a rule, 4 mg/day were administered.

In cases of amenorrhea we rarely found biphasic reactions (4 among 37). The comparison of Ro 4-8347 with epiestriol and clomiphene is not possible because of the small number of cases. Such comparisons seem to be worthwhile. HMG-HCG is of greater efficiency. In 3 gonadotropin-treated women with amenorrhea for many years, who did not show reactions to Ro 4-8347, we induced ovulation and there was conception.

Patients with functional sterility offer much better conditions. The frequency of biphasic reactions amounted to 36 in 58 treatments. The heterogeneity of the cases, however, restricts the value of this relation considerably. The same conclusion is also necessary for the rate of conceptions. Only by analyzing the gonadotropin excretion before, during and after the treatment, every second or third day, or by double-blind experiments can one get reliable results.

Summary

95 treatments with Ro 4-8347 were carried out on 41 patients. Some of these patients were treated with an epiestriol derivate, clomiphene, or with HMG-HCG at the same time. Comparisons of the effect of both treatments are impossible because of the small number of cases. It seems, however, that the HMG-HCG treatment is more efficient in amenorrhoic patients.

The frequency of biphasic reactions in functional sterility was 36 during 58 treatments. To give reliable results about the induction of ovulation by Ro 4-8347 is only possible by analyzing the gonadotropin excretion in the urine every 2 to 3 day or by doing a double-blind experiment.

Author's address: Prof. Dr. H. J. Staemmler, Städtische Frauenklinik, Bremserstrasse 79, D 67 Ludwigshafen am Rhein.