

Zeitschrift:	Bulletin der Schweizerischen Akademie der Medizinischen Wissenschaften = Bulletin de l'Académie suisse des sciences médicales = Bollettino dell' Accademia svizzera delle scienze mediche
Herausgeber:	Schweizerische Akademie der Medizinischen Wissenschaften
Band:	25 (1969)
Artikel:	Central and peripheral action of some progestational steroids
Autor:	Mancuso, S. / Moneta, E.
DOI:	https://doi.org/10.5169/seals-307786

Nutzungsbedingungen

Die ETH-Bibliothek ist die Anbieterin der digitalisierten Zeitschriften auf E-Periodica. Sie besitzt keine Urheberrechte an den Zeitschriften und ist nicht verantwortlich für deren Inhalte. Die Rechte liegen in der Regel bei den Herausgebern beziehungsweise den externen Rechteinhabern. Das Veröffentlichen von Bildern in Print- und Online-Publikationen sowie auf Social Media-Kanälen oder Webseiten ist nur mit vorheriger Genehmigung der Rechteinhaber erlaubt. [Mehr erfahren](#)

Conditions d'utilisation

L'ETH Library est le fournisseur des revues numérisées. Elle ne détient aucun droit d'auteur sur les revues et n'est pas responsable de leur contenu. En règle générale, les droits sont détenus par les éditeurs ou les détenteurs de droits externes. La reproduction d'images dans des publications imprimées ou en ligne ainsi que sur des canaux de médias sociaux ou des sites web n'est autorisée qu'avec l'accord préalable des détenteurs des droits. [En savoir plus](#)

Terms of use

The ETH Library is the provider of the digitised journals. It does not own any copyrights to the journals and is not responsible for their content. The rights usually lie with the publishers or the external rights holders. Publishing images in print and online publications, as well as on social media channels or websites, is only permitted with the prior consent of the rights holders. [Find out more](#)

Download PDF: 16.02.2026

ETH-Bibliothek Zürich, E-Periodica, <https://www.e-periodica.ch>

Istituto di Clinica Ostetrica e Ginecologica (Prof. A. Bompiani),
Università Cattolica del Sacro Cuore, Roma

Central and Peripheral Action of Some Progestational Steroids

S. MANCUSO and E. MONETA

It seems already established by different groups of investigators that the majority of progestational steroids, associated with estrogens or not, exerts an inhibitory effect on the secretion and/or production of pituitary gonadotrophins.

This inhibitory effect would result in a block of the pituitary-ovarian axis with consequent suppression of ovulation. This is accepted as a mechanism of action common to most of the steroids employed for the control of fertility. This subject has been recently and extensively reviewed by DICZFALUSY (1968).

The discontinuation of a long term treatment with progestational compounds alone or associated with estrogens in a continuous or sequential form, may result in an enhanced fertility, the so-called "rebound effect". Whereas this phenomenon has been constantly observed after the discontinuation of a sequential type of medication, as reported by GOLDZIEHER et al. (1964), in many cases of continuous treatment or treatment with progestational compounds alone, there have been numerous reports describing long lasting amenorrhoea or menstrual disorders or infertility at the end of the medication (WHITELOW et al., 1966).

In this connection it seems of interest to mention one case, which has been observed in our department.

A young lady, aged 25, partially hypophysectomized in 1961 (when she was 17) because of a calcified glioma of the third ventricle had a secondary amenorrhoea since the time of the operation.

Three years after the operation she was treated with a continuous type of estrogen-progestational therapy for five cycles (vinylestrenolone 5 mg + ethynodiol diacetate 0.075 mg), and the amenorrhoea persisted after discontinuation of the treatment.

Four years after the previous medication she came to our clinic and at that time she showed no FSH or LH peaks in the urine and the mean of the basal values were respectively 6.5 and 14.0 IU/24 h. She was treated with a sequential therapy for three cycles according to the following scheme: ethynodiol diacetate 0.025 mg from day 1 to 7, then 0.100 mg from day 8 to 21 and finally 0.125 mg associated with medroxyprogesterone 10 mg from day 22 to 28.

Since the discontinuation of the medication the patient has been normally menstruating for two cycles. The subsequent cycles are being presently studied to assess ovulation.

It can be assumed in this case that the suspension of the sequential type of therapy may have induced a "rebound effect", maintaining a long term cyclic equilibrium between FSH and LH. This "rebound effect" is presently being studied in two more amenorrhoeic, partially hypophysectomized patients, treated with the same type of sequential therapy by means of the daily determination of urinary gonadotrophins FSH and LH.

It has been reported by DICZFALUSY (1968) that when progestational compounds are given alone they generally suppress the midcyclic peak of LH without necessarily interfering with the FSH peak. This seems to be directly related to the dose administered. In fact daily doses of progestational steroids below 1 mg effect less the pituitary gonadotrophins and due to the treatment many ovulatory cycles are observed in patients who are nevertheless infertile (ELSTEIN, 1969). In these cases the mechanism of action of low doses of progestational compounds seems to be mainly at a peripheral level: endometrium or cervical mucus (DICZFALUSY, 1965).

It is still under discussion whether or not low doses of progestational compounds would interfere with the enzymic mechanism responsible for the synthesis of progesterone in the corpus luteum, because very low values of urinary pregnanediol have been observed in normally ovulating patients, treated with 0.5-0.3 or 0.2 mg of chlormadinone acetate or norgestrel (FOTHERBY, 1969). Moreover it seems that progestational compounds do not interfere with the excretion of pregnanediol, after i.m. administration of progesterone (ØSTERGAARD and STARUP, 1968).

We have some evidence which would support this view. A corpus luteum taken at laparotomy, after three cycles of treatment with chlormadinone acetate (0.5 mg in daily administrations) was incubated with pregnenolone- 7α - 3 H. In the neutral fraction of the extract, huge amounts of 17α -hydroxyprogesterone were isolated and identified, whereas this compound was almost undetectable in a control corpus luteum of the same life span, taken at laparotomy from an untreated patient and incubated with the same precursor under identical experimental conditions. On the other hand, much less progesterone was formed in the corpus luteum of the patient treated with chlormadinone acetate, from 3 H-labelled pregnenolone, compared with the control corpus luteum. Urinary determinations of pregnanetriol are now in progress in all the patients treated with chlormadinone acetate, to establish also the increase in the output of this catabolite of 17α -hydroxyprogesterone. On the basis of these preliminary results, one could think of a preferential activation of the 17α -hydroxylation respect to the conversion to Δ^4 -3-keto compounds from pregnenolone, which is normally the direct precursor of the ovarian progesterone (Fig. 1).

Some derivatives of retroprogesterone are progestational compounds and present very interesting characteristics. Dydrogesterone does not inhibit ovulation, according to BISHOP et al. (1962), and seems to have a mild

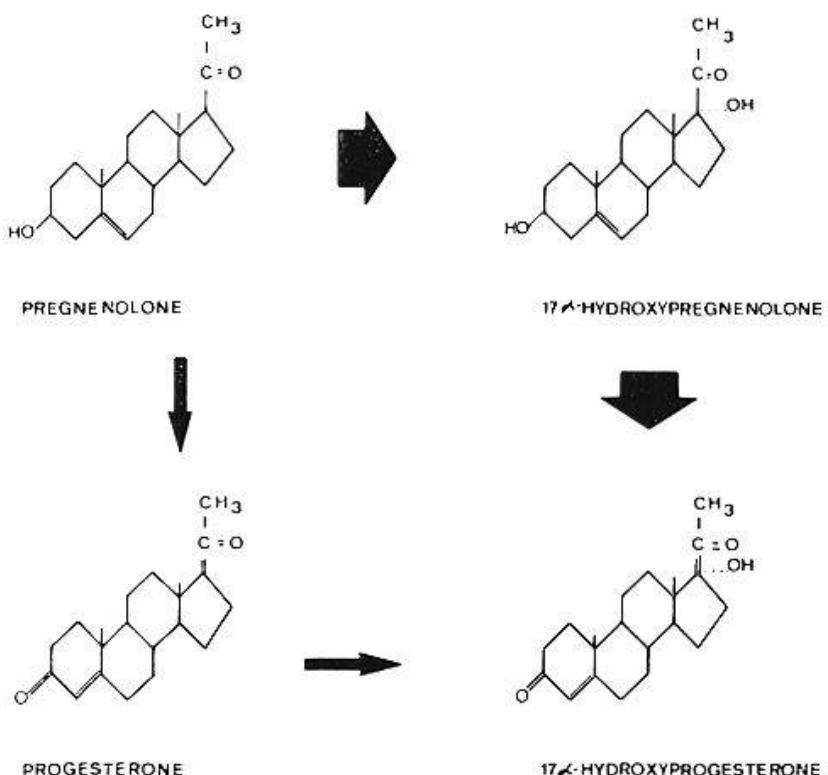


Fig. 1.

inhibitory effect on pituitary gonadotrophins, according to BELL and LORAINNE (1965). Although in some patients they noted a marked "rebound effect" on the total excretion of urinary gonadotrophins in the cycle following the discontinuation of therapy. The same authors reported in 1967 a marked and immediate "rebound effect" in 1 of 2 postmenopausal women treated with SAZL-121 (Philips-Duphar), compound which is structurally related to Duphaston.

The compound Ro 4-8347 (6-chloro-9 β ,10 α -pregna-1,4,6-triene-3,20-dione) has been recently studied, showing a direct influence on the regulation of gonadotrophin release and induction of ovulation in amenorrheic patients (GERHARD and STAMM, 1969; STAMM et al., 1968).

We have employed this compound in 5 cases of secondary amenorrhoea and after treatment, in two of these patients, corpora lutea have been found at laparoscopy and laparotomy. Furthermore in one case of anovulatory cycles with primary sterility lasting 6 years, after ten days of treatment with this compound at a dosage of 8 mg per day the patient became pregnant and she is presently at the 12th week of gestation.

Fig. 2 illustrates the results obtained by the treatment with Ro 4-8347 of one of our patients. Amenorrhoeic since June 1968, she was operated in November 1968 and a large follicular cyst was removed from the left ovary. The amenorrhoea persisted after the operation and she started the treatment at the end of January (8 mg/day for 15 days). After the first menstruation she had additional treatment from the 11th to the 13th day of the cycle with 8 mg/day.

From the different parameters studied in this patient, it can be seen that

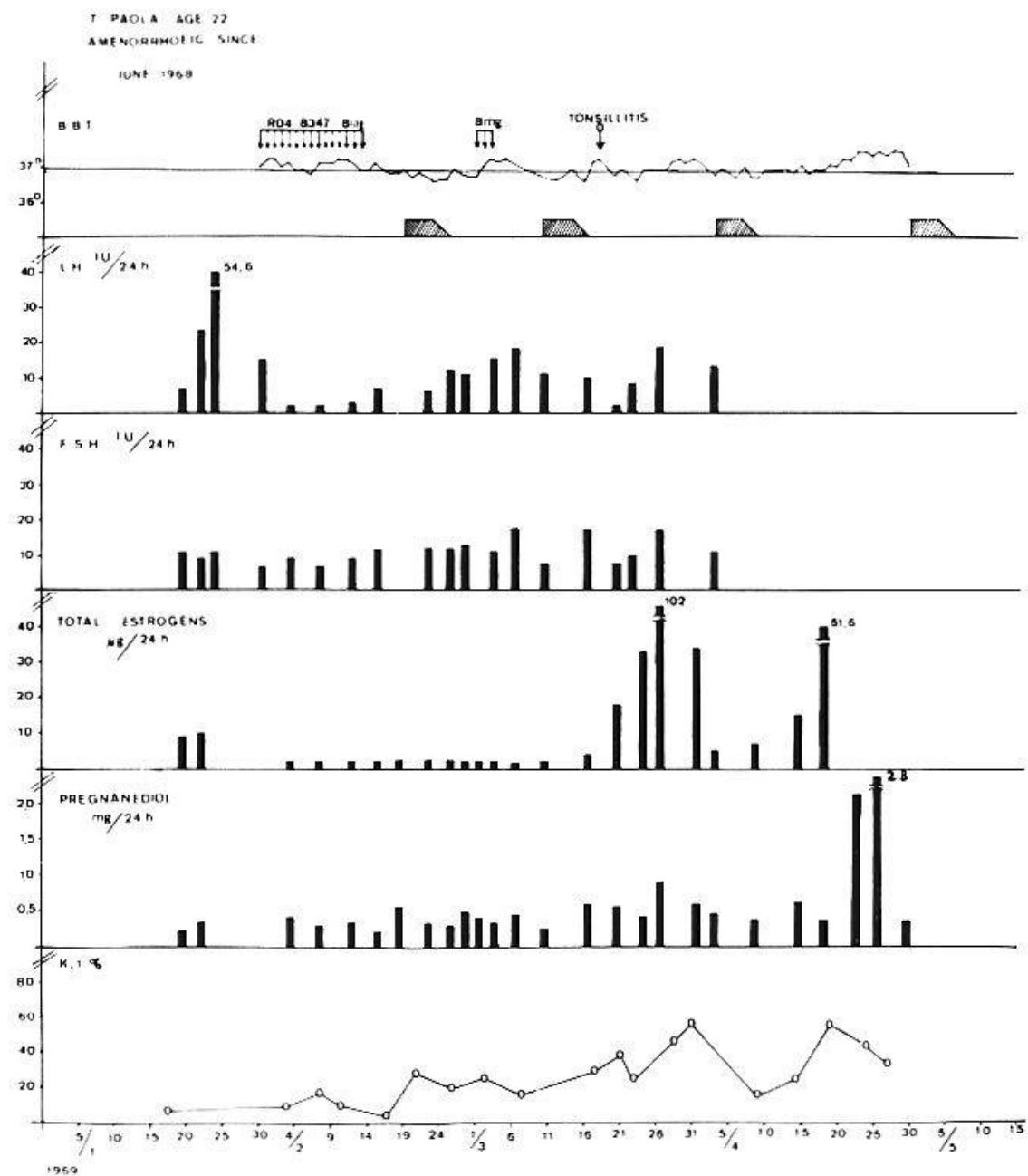


Fig. 2.

after the treatment both FSH and LH have a cyclic pattern, that the basal temperature becomes biphasic, and the estrogens, pregnanediol and vaginal smears show that the cycles have an ovulatory character.

Conclusions

After discontinuation of a sequential type of treatment a "rebound effect" may be induced, followed by the cyclic production of gonadotrophins and the regulation of menstruation.

Progestational compounds alone at high dosage interfere with the mid-cyclic peak of LH and, consequently, with ovulation, whereas at low dosage

their action is mainly peripheral. There are reasons to believe that the biosynthetic pathway leading to the formation of the ovarian progesterone is altered in one or more steps.

Finally, the retroprogestational agents can produce an immediate "rebound effect" as seen in the excretion of gonadotrophins. And in the case of compound Ro 4-8347 there is a direct stimulatory effect on the release and/or production of both FSH and LH which can be successfully utilized in therapy.

The present state of research in the field of control of reproduction in many countries calls for careful controlling of the moment of ovulation. With the aid of compounds which can influence the pituitary-ovarian axis, this may become a real possibility in the near future. In view of our data available at present, we are testing the value of compound Ro 4-8347 in regulating the midcyclic peak of LH and therefore the day of ovulation in normally menstruating women.

Acknowledgements. We are indebted to Drs. P. DONINI and SILVIA DONINI for the determinations of urinary FSH and LH. - Part of the expenses for this investigation were defrayed by Grant No. M 67-139 from the Population Council and by Research Grants from Syntex and Hoffmann-La Roche.

BELL E. T. and LORAIN J. A.: *Lancet* 1965/I, 403.
BELL E. T. and LORAIN J. A., in: *Recent Research on Gonadotrophic Hormones. Proceedings of Fifth Gonadotrophin Club Meeting, Edinburgh 1966*, p. 243. Livingstone Ltd., Edinburgh/London 1967.
BISHOP P. M. F., BORELL U., DICZFALUSY E. and TILLINGER K.-G.: *Acta endocr. (Kbh.)* 40, 203 (1962).
DICZFALUSY E.: *Brit. med. J.* 1965/II, 1394.
DICZFALUSY E.: *Amer. J. Obstet. Gynec.* 100, 136 (1968).
ELSTEIN, M., in: *Chlormadinone Acetate. A new departure in oral contraception* (ed. by G. A. CHRISTIE and M. MOORE-ROBINSON), p. 46. Excerpta Medica Foundation, Amsterdam 1969.
FOTHERBY K., in: *Chlormadinone Acetate. A new departure in oral contraception* (ed. by G. A. CHRISTIE and M. MOORE-ROBINSON), p. 108. Excerpta Medica Foundation, Amsterdam 1969.
GERHARD I. and STAMM O.: *Gynaecologia* (Basel) 168, 25 (1969).
GOLDZIEHER J. W., BECERRA C., GUAL C., LIVINGSTON N. B. jr., MAQUEO M., MOSES L. E. and TIETZE C.: *Amer. J. Obstet. Gynec.* 90, 404 (1964).
ØSTERGAARD E. und STARUP J.: *Acta endocr. (Kbh.)* 57, 386 (1968).
STAMM O., CAVENG B., GERHARD J. and KELLER M.: *Geburtsh. u. Gynäk.* 169, 225 (1968).
WHITELAW M. J., NOLA V. F. und KALMAN C. F.: *J. Amer. med. Ass.* 195, 780 (1966).

Authors' address: Prof. Dr. S. Mancuso, Dr. E. Moneta, Università Cattolica del Sacro Cuore, Facoltà di Medicina e Chirurgia, Istituto di Clinica Ostetrica e Ginecologica, Via della Pineta Sacchetti 644, Rome/Italy.

Discussion

J. HAMMERSTEIN: I would like to comment on your incubation study: 1. There could be another interpretation. I think it is possible that in this treatment nothing else happened than a fast transformation from pregnenolone to 17-hydroxy-progesterone. We have found a similar thing in the presence of clomiphene. 2. We always use the slicing technique and find that progesterone is the most prominent labelled steroid in human corpora lutea. Are you using homogenates?

S. MANCUSO: Yes. What precursor have you used?

J. HAMMERSTEIN: It is independent from whether we use pregnenolone or acetate. 3. When we in our experiments with clomiphene compared the parallel incubation from the same corpus luteum either with acetate or with pregnenolone and progesterone as precursors, we found that even if there was a piling up of labelled steroids such as 17-hydroxy-progesterone, using the latter two precursors, we could not find the same with acetate, so I think one should be very careful in the interpretation when using precursors like pregnenolone.