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Influence on Gonadotropins by Progestational Agents

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Although the corpus luteum was already described by de Graaf in 1672, its endocrine function was observed for the first time 200 years later. This endocrine effect was the characteristic influence on the estrogen-primed endometrium. Several groups isolated in 1934 the biologically active pure crystalline compound for which the name progesterone was adopted. The number of progestins increased between 1945 and 1966 from 2 to 20. Experiments with the different compounds showed that the biological effect differs more or less extensively either in quality or intensity. One must keep in mind that the term progestin means that the substance is responsible for the secretory response of the estrogen-primed endometrium. Therefore, one cannot expect that compounds having this biological effect in one target organ, have the same effect in other organs or on other biological systems. Today it is, therefore, not possible to give a definite summary of the effect of progestins on gonadotropins, neither the release, the production nor the action. The best known effect in this respect is the negative feedback mechanism of ovarian steroids on gonadotropin secretion rates. But what I would like to discuss are the positive or regulating effects of progestins on gonadotropin function.

In clinical observations it was noted that the use of progesterone or other luteoid substances in the control of bleeding in patients with anovulation is followed occasionally by ovulation and the formation of a corpus luteum. On the other hand, it is well known that in the normal menstrual cycle progesterone excretion begins to increase at or after the midcycle LH peak. Recently it was shown that 17α-hydroxyprogesterone levels rise 2–3 days before the progesterone.

Therefore, there are two reasons to study the influence of progestins on gonadotropins. First, the not completely understood relationship between progesterone- or similar steroids and FSH and LH effects. Secondly, clinical observations on results of progestin treatment in anovulatory patients.

Investigations of the influence of progestational agents on ovulation indicate a specification of response to ovarian reaction of the animal under observation. Basic laboratory research intended to clarify the ovulatory

mechanism showed wide differences in the several species of animals studied in neural, humoral and physical respects. Progesterone may play an important role in the induction of ovulation in several groups of experiments involving a variety of laboratory animals. There are experiments which give evidence for the induction of ovulation through the administration of progesterone in the domestic hen, turkey, monkey, mouse, rat and rabbit. It appears from these studies that the effectiveness of progesterone is mediated through the hypothalamus with subsequent release of pituitary LH. But current evidence seems to indicate that receptors for progesterone and estrogen with respect to their actions on pituitary function are located in both the anterior pituitary and the hypothalamus.

In numerous experiments with several species of animals an effect on gonadotropin function could be demonstrated. The effects of steroid hormones on gonadotropin secretion rates have been assessed by measuring gonadotropin levels in the pituitary, the blood and the urine. Everett (1943) found in rats that a single injection of progesterone at certain times may cause a release of pituitary luteinizing hormone. In the estrous or estrogen treated rabbit, progesterone exerts a biphasic effect on the threshold of pituitary activation (Sawyer, 1961). The injection of 2 mg of progesterone was followed by a lowering of the threshold. However, 24 h after progesterone treatment the pituitary activation was highly elevated. In respect to pituitary activation there appears to be a biphasic effect of progesterone. Rothschild (1962) assayed the gonadotropin potency in pituitaries of rats and found that pituitaries of rats treated with 1 mg of progesterone were slightly more potent than those of untreated rats. These results were interpreted as evidence that progesterone does not inhibit gonadotropin formation but only the release. Similar results were found with the synthetic compound norethinodrel (Brown et al., 1965). In the latter only minor effects were seen on the FSH content in rat pituitaries. But when LH was tested, the pituitary tissue from rats treated with norethinodrel was more potent than the tissue from control rats. These results suggest a change in the FSH/LH ratio. In castrated rats bearing ovarian autotransplants, progesterone treatment was associated with a significant elevation of pituitary gonadotropin potency (Kaufmann and Rothschild, 1966). It seems that specifically the acute release of an ovulation inducing hormone, i.e. LH, was inhibited by progesterone. In progesterone-treated intact rats the hypophyseal LH potency was maintained during progesterone treatment at a level equivalent to that of cyclic rats (Rothschild and Schwarz, 1965). In the absence of peripheral measurements of gonadotropins in the animal receiving the steroid being tested, whether changes of pituitary hormone content are due to changes in the rate of synthesis and the rate of release, cannot be distinguished (Schwartz, 1968).

This is why the amounts of gonadotropins in plasma were determined, since they represent an ideal approximation of gonadotropin secretion rates. Nallar et al. (1966) found 6 h after the injection of progesterone an eleva-

tion of plasma LH when the injections were given in late di-estrous or in pro-estrous during the normal cycle. This effect was not seen in estrous and in early di-estrous, and progesterone was without effect on plasma LH in ovariectomized rats. That means that progesterone stimulates LH release when administered during the preovulatory phase of the rat's estrous cycle. In ovariectomized, estrogen-treated rats progesterone injection on the 3rd day after estrogen also induced an increase in plasma LH a few hours later (CALIGARIS, 1968). These experiments further showed that following a period of stimulation of LH release an inhibitory status is established. As ovariectomized rats failed to respond to progesterone by a rise in plasma LH, previous treatment with estrogen seems to be necessary to make sensitive the animals to the stimulation of progesterone.

Several authors studied the influence of progestational agents on exogenous gonadotropins. In immature rats progesterone had no effect on the sensitivity of the ovary to PMS (WYSS and PINCUS, 1964). SMITH and BRADBURY (1966) found that progestin influenced ovarian function by modifying the elaboration of endogenous pituitary gonadotropin. In this paper it was stated that progestin probably modifies the release of pituitary LH. The effect of HCG on uterine weight was enhanced by chlormadinone (HARPER, 1965). Progesterone, when superimposed on PMS, had no significant effect on plasma or pituitary LH levels. However, progesterone blocked the release of FSH caused by PMS whether PMS was given alone or followed by HCG treatment (CALANTINE and HUMPREY, 1965).

Recently we have studied the influence of progesterone and 6-chloro-9β,10α-pregna-1,4,6-triene-3,20-dione (Ro 4-8347) on the effect of PMS in the mouse uterus test and the augmentation test and also on the effect of HCG in the ovarian ascorbic acid depletion test. First, it could be shown in ovariectomized mice that both steroids were antiestrogenic. By the administration of 0.1 mg Ro 4-8347 the influence of 0.09 μg estradiol on uterine weight was inhibited more than 50 %. Progesterone in comparison with the retroprogesterone seems to have a stronger anti-estrogenic effect (Fig. 1). In the mouse uterus test in intact immature animals with PMS 0.1 mg, both steroids did not influence the increase in uterine weight. When the dosage was increased to 0.5 mg we found a significantly lower increase in the uterus weight. With 0.5 mg the gonadotropin effect was almost completely suppressed (Fig. 2). In the third experiment the influence of progesterone and Ro 4-8347 was studied in the augmentation test (Fig. 3). With the lowest dosis of PMS, i. e. 5 IU, an inhibition occurred. With 10 IU PMS no significant effect of progesterone could be found, but different doses of the retroprogesterone had a negative effect on the increase in ovarian weight. With higher amounts of gonadotropin no effect was seen. At last the influence of progesterone and Ro 4-8347 on the ovarian ascorbic acid depletion test was studied. The test was done with 3, 6 and 12 IU HCG.The progestins were given 3 h and 12 h, respectively, before the test. In the 3-h-experiments (Fig. 4) the LH effect was lowered by both progestins and with all doses used. There

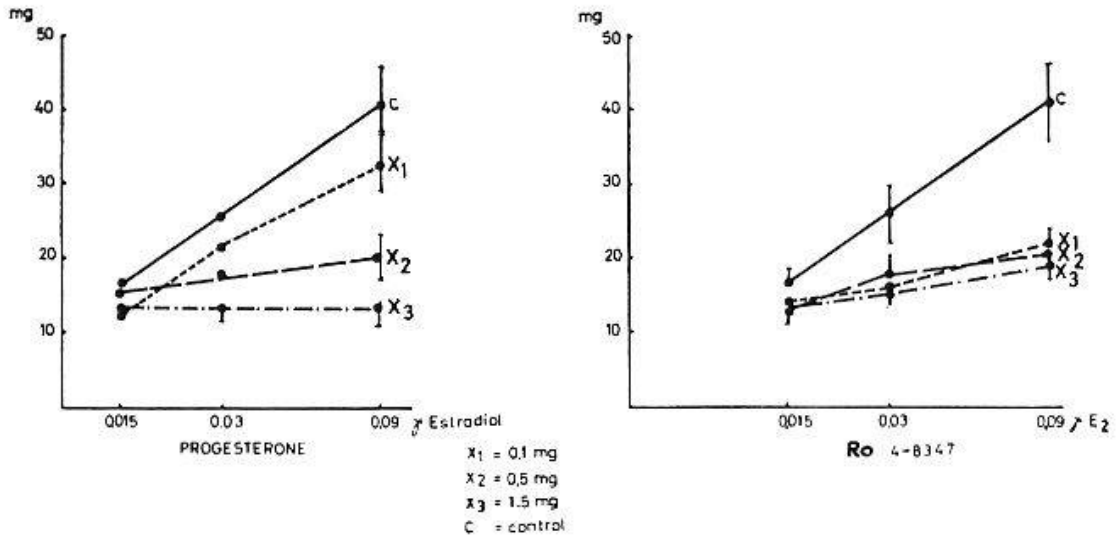


Fig. 1. Mouse uterus test (ovariectomized mice).

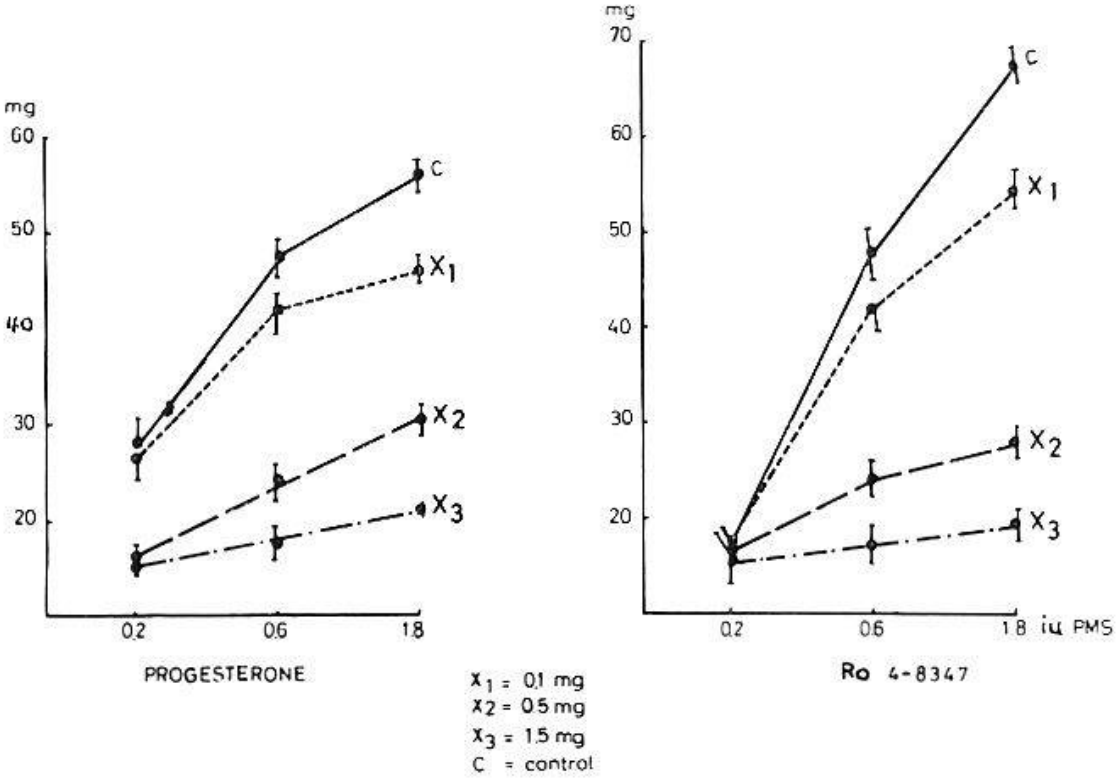


Fig. 2. Mouse uterus test.

were no marked differences between the two steroids. Only in the group with 12 IU HCG was the inhibition smaller after administration of the retroprogesterone compared to progesterone. When the progestins were administered 12 h before the OAAD, test differences between progesterone and retroprogesterone were found (Fig. 5). The LH effect was not influenced by progesterone, but the retroprogesterone enhanced the LH effect. A quantitative relationship was seen only in the group of animals which received 3 and 6 IU HCG but not after the administration of 12 IU HCG.

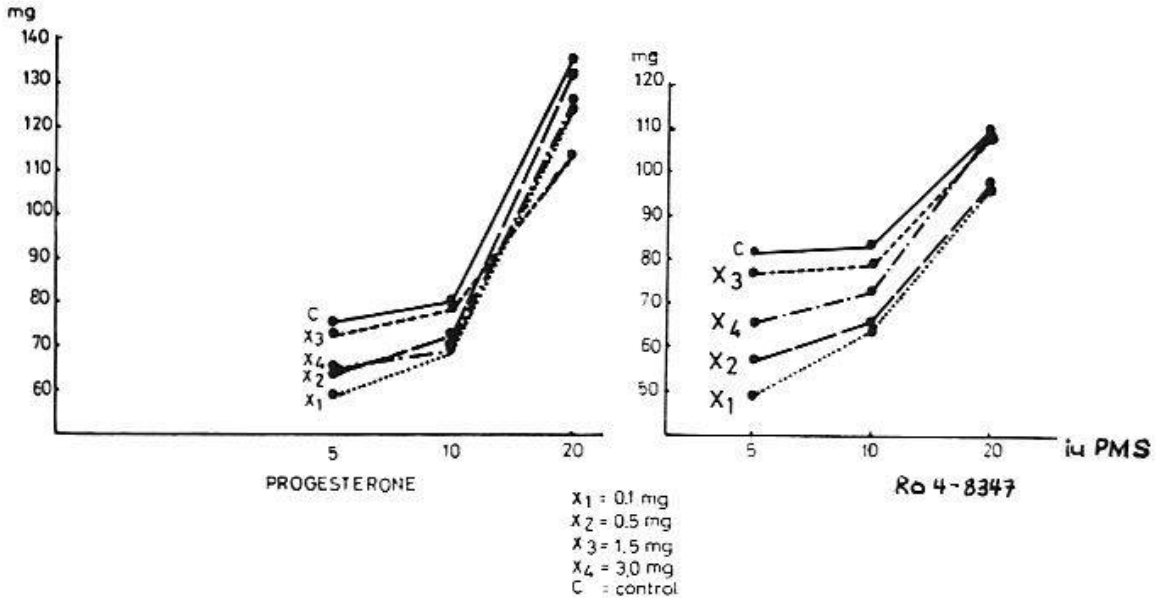


Fig. 3. Augmentations test.

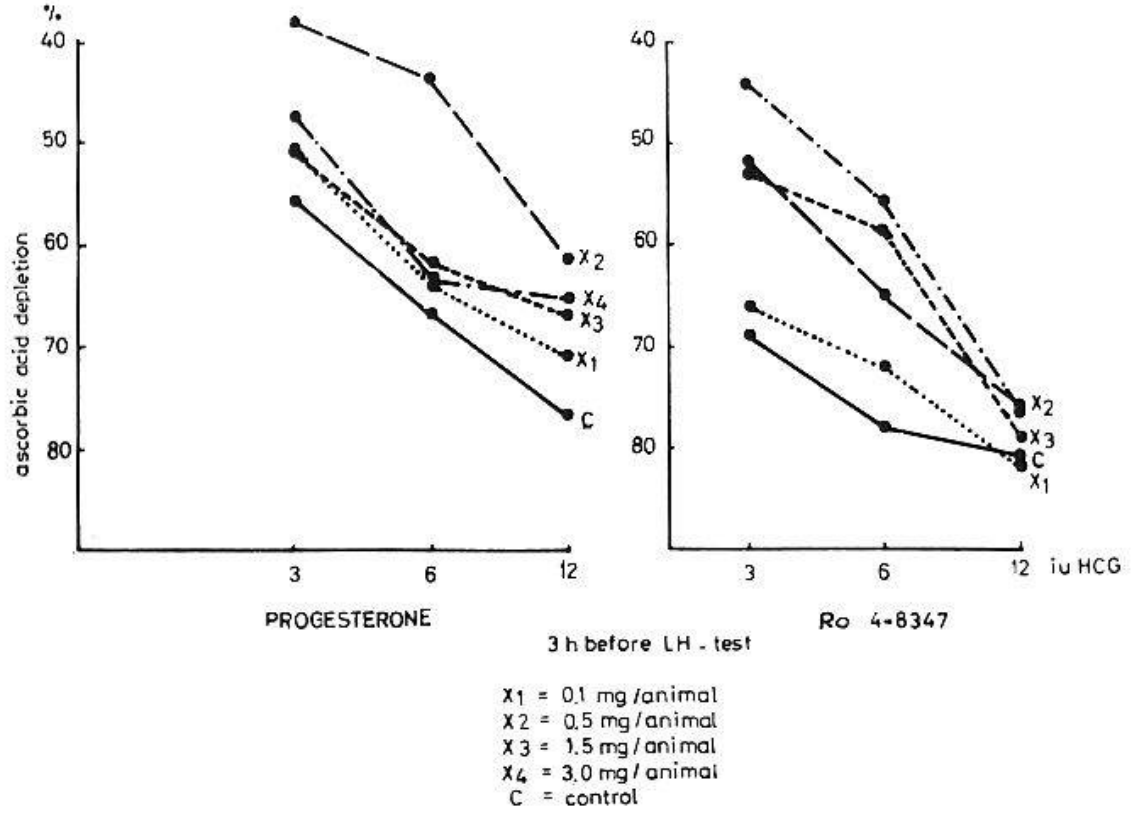


Fig. 4. Influence of progesterone or Ro 4-8347 on ovarian ascorbic acid depletion test.

From the studies in animals we have to conclude that there are positive effects on gonadotropin action. First, the production or release of pituitary gonadotropins is influenced probably by altering the ratio of FSH to LH. A prerequisite for this effect seems to be a final endocrine status, either within a set time during the ovarian cycle, or due to a definite pretreatment

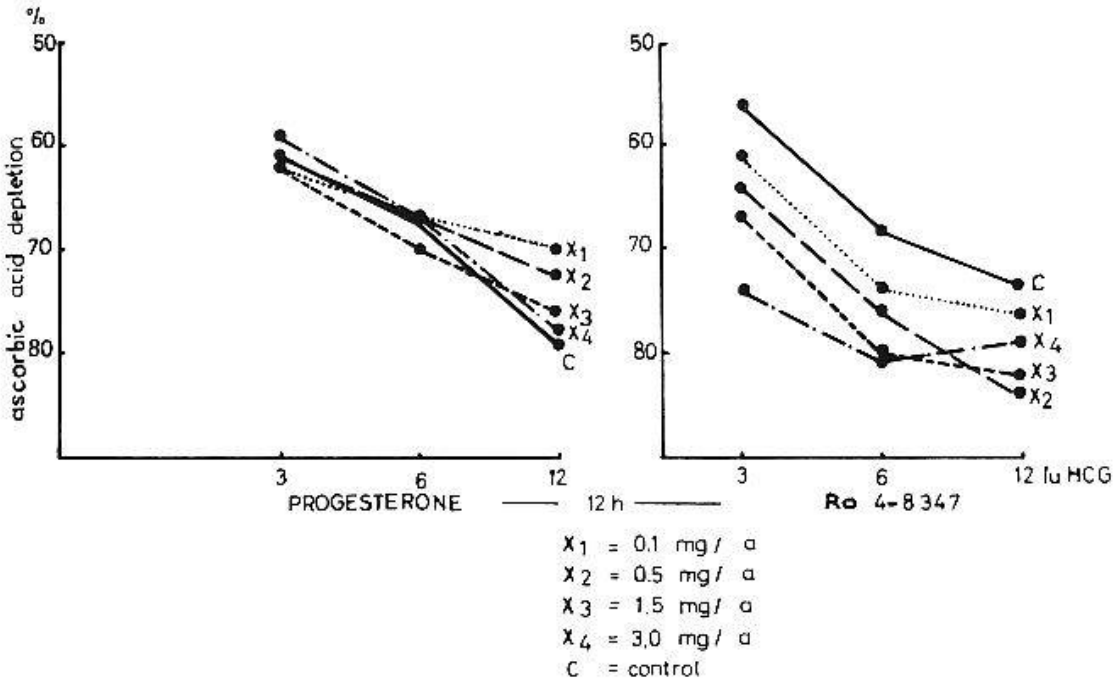


Fig. 5. Influence of progesterone or Ro 4-8347 on ovarian ascorbic acid depletion test.

with estrogens. Secondly, the effect of exogenous gonadotropin also is influenced by different progestational agents. In definite conditions progestins can have a positive influence on LH action and probably a negative one on FSH.

There are some studies of this problem also in the human. On the whole, these are insufficient and it is not possible to make definite statements. Mainly, the following effects of progestins are important for the clinician: 1. secretory transformation of the endometrium, 2. elevation of the basal body temperature, 3. inhibition of the estrogen effect on cervical mucous and vaginal cells, 4. suppression of ovulation. Only the last effect in which an influence on gonadotropins is involved, is related to the problem which shall be discussed here. But, as I mentioned before, I want to report here only on the positive influences of progestins on gonadotropin action.

The first evidence for such an effect resulted from clinical observations that in anovulatory patients after treatment with progestins sometimes ovulation occurred. Rust (1956) treated 35 patients with anovulatory cycles with 5 mg progesterone for 4 days or 30 mg 17α-hydroxy-progesterone-capronate in the beginning of the cycle and on the 8th day (Fig. 6). In 60% of the treatments ovulation could be induced, 6 patients became pregnant. In 1957, Swartz et al. reported on 15 cases with anovulatory bleedings. Only in one of these did it seem at all likely that progesterone may have triggered the ovulatory mechanism. Holmstrom (1954) used a single dose of 25–50 mg of progesterone in 30 patients with primary amenorrhoea. In 12 patients ovulation occurred in the first 4 months after beginning of the treatment. Rothschild and Koh (1951) reported that the time of ovulation in the human female could be advanced through the use of progesterone.

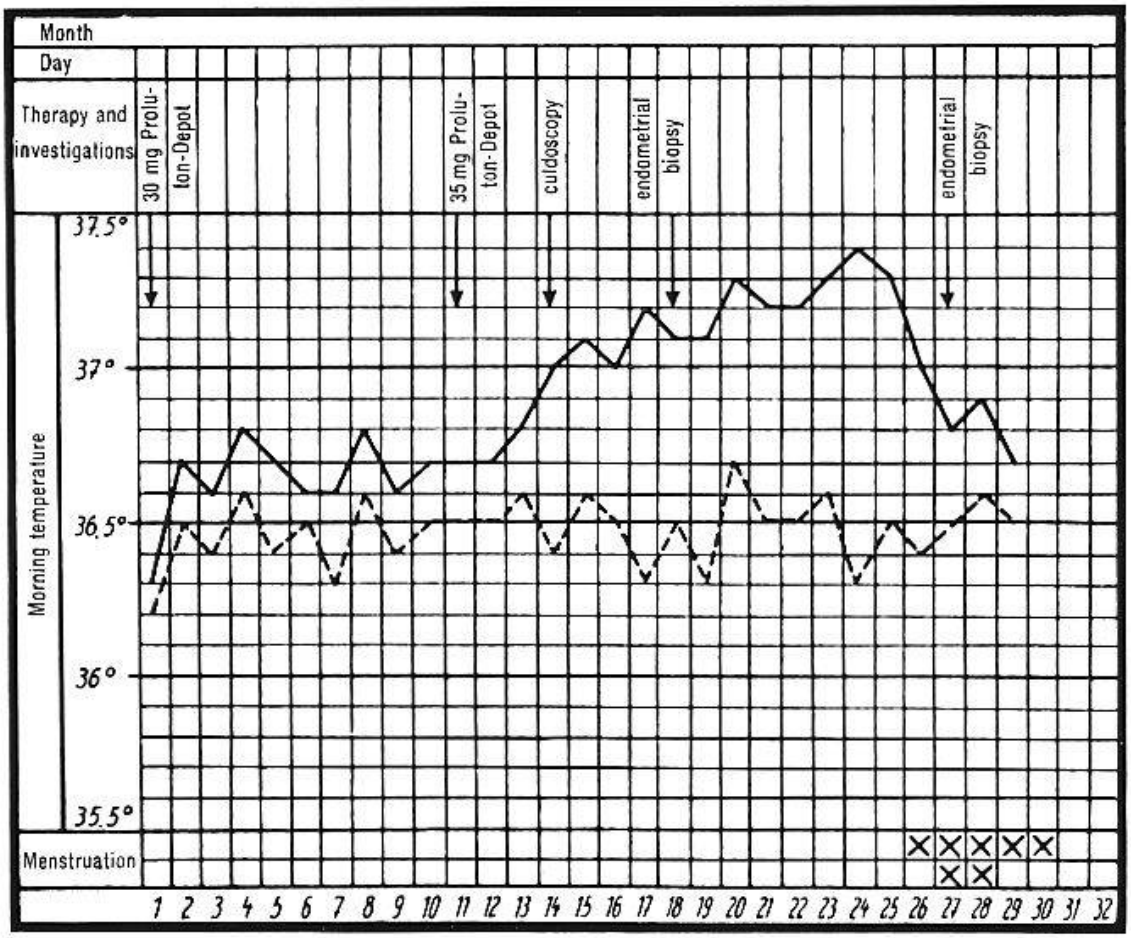


Fig. 6. Typical temperature curve during treatment (——) and the same patient's temperature curve during the previous, untreated month (– – –) (Rust, 1956).

Napp and Rothe (1958) administered small doses of methyl- or ethinyl-nortestosterone to 12 patients with secondary amenorrhoea for 5–6 days (Fig. 7). The authors suggest that four times ovulation was induced. Haskins (1966) used progesterone intravenously or 5 mg norethindrone on 5 days. On a number of occasions this treatment resulted in biphasic temperature curves that could indicate ovulation. The effects of the retroprogesterone will be discussed later in this meeting.

Frequently used in treatment of anovulation is the rebound effect. Ovarian steroids are given over a period of time in the hope that their successive influence and withdrawal might result in the stimulation of the cyclic secretion and release of gonadotropin and in this way reinduce spontaneous ovulation. The results of this therapy have been disappointing. Evans et al. (1967) treated 50 women for 2 months. Spontaneous ovulation occurred within 6 weeks in 25 of them with 9 pregnancies. In a group of 34 patients Hammerstein observed biphasic cycles in 14 patients. It should be mentioned that in this type of treatment progestins were administered in combination with estrogens.

There are some studies on the influence of progestins on gonadotropin excretion in human beings. Holmstrom (1954) found an increase of FSH

after the administration of progesterone. Fuchs et al. (1964) could show that neither the administration of 100 mg of progesterone per day nor that of 6-methyl-17-acetoxy-progesterone was able to inhibit the increase of gonadotropin excretion after the removal of functional ovaries. Buchholz et al. (1964) studied the effect of progesterone on the endocrine activity of the pituitary glands (Fig. 8 a and b). When on the 5th day of the cycle 200 mg of progesterone were injected the urinary excretion of gonadotropins was elevated within the first 24 hours following the injection. The peak was followed by a drop 3 days later. Administration of progesterone on the fourth day before the shift of basal body temperature was also followed by an increase in urinary gonadotropins for 3 days. This increase was markedly less than in the first group. However, a second peak in gonadotropins occurred 10 days after injection. From these experiments it was concluded that ovulation by no means occurred earlier, but more likely was considerably retarded.

Recently Swerdloff and Odell (1968) could demonstrate that in 4 of 8 subjects an LH peak occurred under the administration of sequential contraceptives immediately after the addition of progesterone (Fig. 9). No FSH peak was noted. In other experiments Odell has shown (1968) that after an appropriate period of administration of estrogen to postmenopausal women a single dose of 10 mg progesterone resulted in an elevation of plasma LH and FSH similar to the midcycle peak of an ovulatory cycle. This peak lasted 24–72 h. Compared to the control following progesterone FSH activity was lower than LH. No such a peak could be found in men.

Several authors have studied the influence of progestins on exogenous gonadotropins in female patients. Staemmler (1960) found that 100 mg ethinyl-nortestosteron-enanthate did not influence ovulation induced by PMS-HCG treatment. Administration of 200 mg ethinyl-nortestosterone-enanthate or daily 12 mg ethinyl-nortestosterone-acetate abolished the effect of PMS-HCG therapy. Gemzell (1960) administered 100 mg progesterone together with HPFSH to 5 amenorrhoic women (Fig. 10). In 2 the urinary estrogen rose, but in no case was ovulation induced. We have studied (Bettendorf, 1963) the effect of 20 mg 17α-ethinyl-nortestosterone together with human hypophyseal gonadotropins in one hypophysectomized patient. The patient responded with ovulation on gonadotropin treatment, but after adding the progestin only a rise in estrogen excretion occurred. In another patient with secondary amenorrhoea during 8 days HHG was given, then 5 days the same dose in combination with 20 mg ethinyl-nortestosterone (Fig. 11 and 12). No ovulation was induced. In a second course only the estrogen levels showed an increase. The stimulation of estrogen production by gonadotropin treatment was not influenced by the progestin, but there was no induction of ovulation. Lunenfeld (1964) used HMG together with 6α-methyl-17α-acetoxy-progesterone. 5 mg of this substance did not effect the ovarian response to exogenous gonadotropins. However, the administration of the progestin together with ethinylestradiol resulted

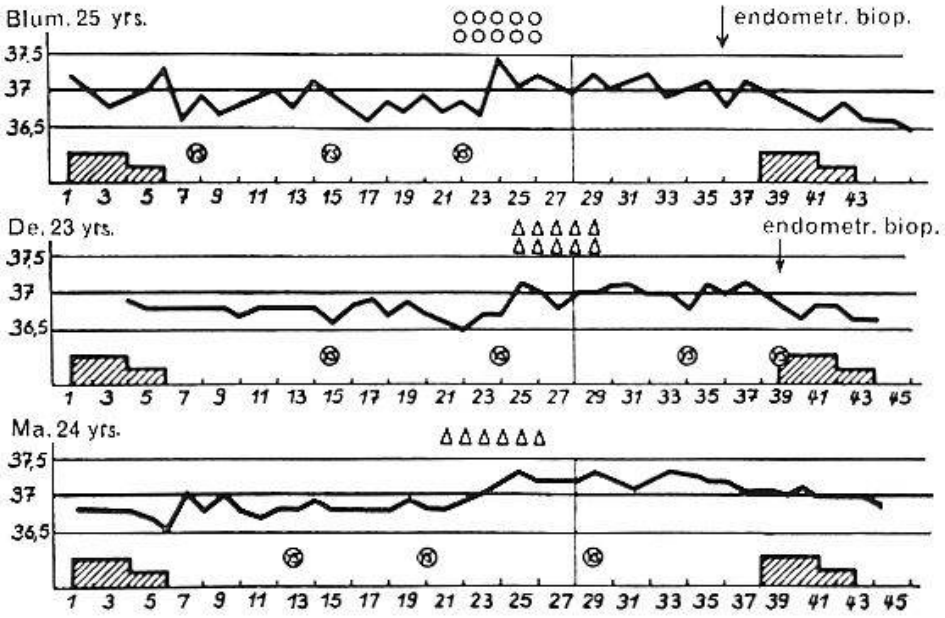
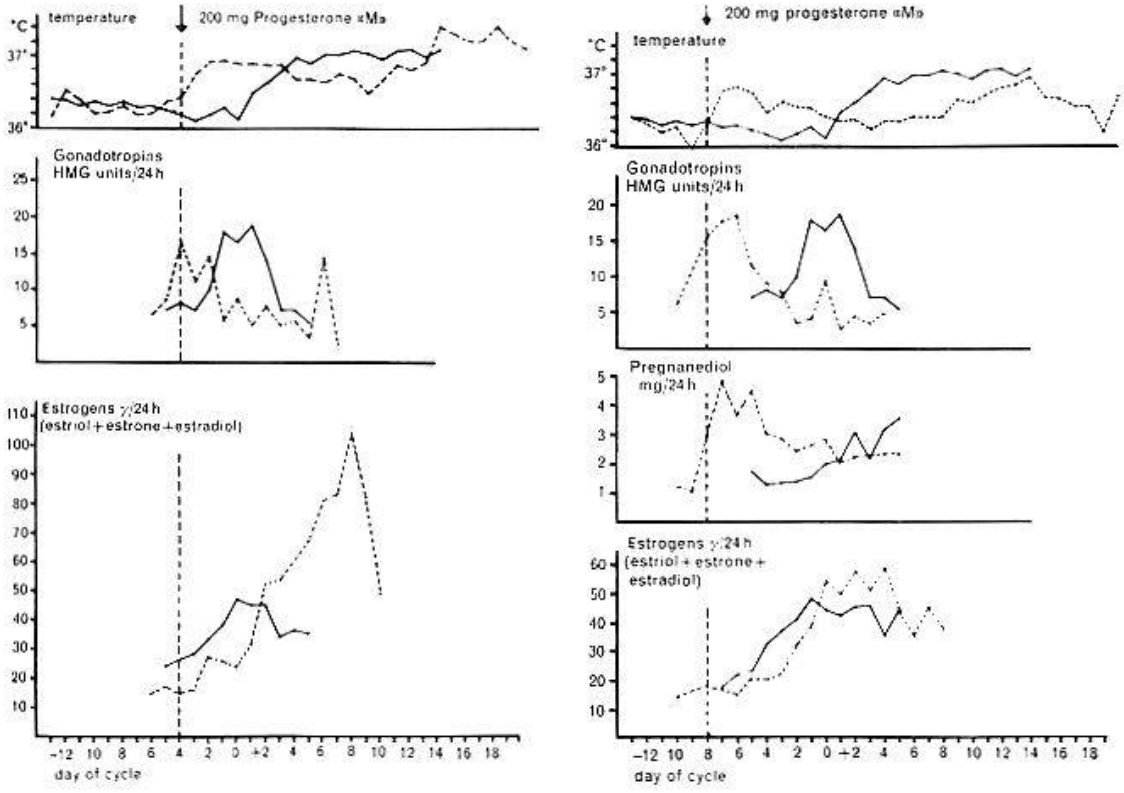


Fig. 7. Induced ovulation with nortestosterone compounds. △ = 1 mg tablets of ethinyl-nortestosterone (Primolut N); ○ = 1 mg tablets of methyl-nortestosterone (Orgasteron) (NAPP et al., 1958).



a b

Fig. 8. – a) Effect of microcrystalline progesterone administered on the 5th day following onset of menstruation on the urinary excretion of pituitary gonadotropins, pregnanediol, and estradiol + estrone + estriol in group VI. – b) Effect of microcrystalline progesterone administered on the 4th day before zero on the urinary excretion of pituitary gonadotropins and of estradiol + estrone + estriol in group VII (BUCHHOLZ et al., 1964).

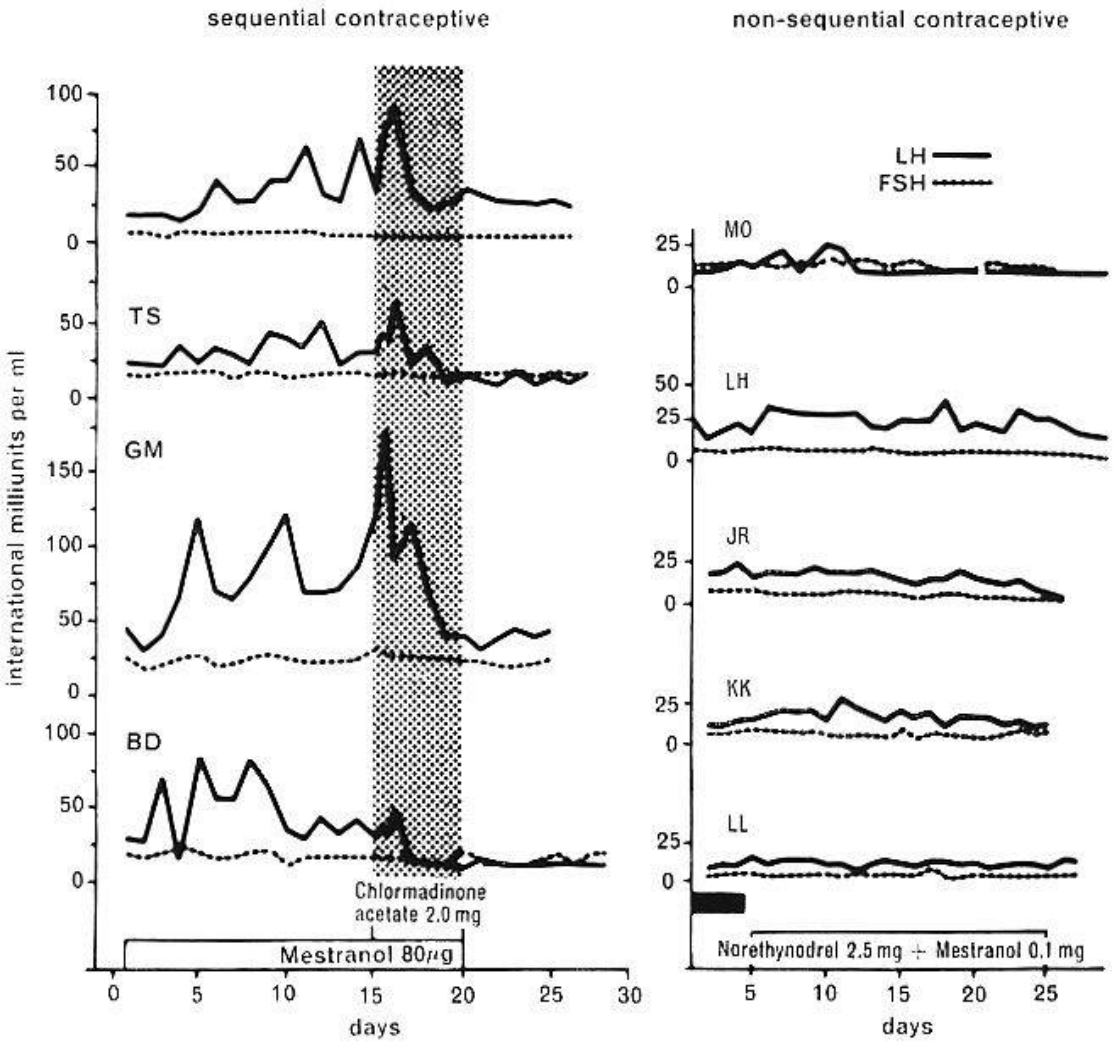


Fig. 9. Daily FSH and LH determinations on serum from 4 women receiving a sequential estrogen-progestogen contraceptive and from 5 women receiving a non-sequential estrogen-progestogen contraceptive. These examples were selected from a total of 6 that we have studied and who received the latter and 8 who received the former type of contraceptive (SWERDLOFF and ODELL, 1968).

in inhibition of the ovarian response to the gonadotropins, even when extremely high doses were administered. When 2 patients by TAYMOR (1965) were placed on norethindroneacetate (5 mg) along the urinary gonadotropins the evidence of ovarian activity persisted (Fig. 13). That means that a dosage which is capable of inhibiting ovulation in normally ovulating females is incapable of blocking the response of ovaries to administered gonadotropins. Also GUAL et al. (1968) (Fig. 14 a and b) found that in some cases successive exogenous gonadotropin stimulation is able to induce ovulation even when administered simultaneously with antiovulatory steroid.

In the proceeding discussion of the effects of progestins on gonadotropin function it was not possible to delineate the sites of action of these steroids. There are three groups of effects which suggest a regulating influence on gonadotropin action: 1. clinical studies of progestin-induced ovulation,

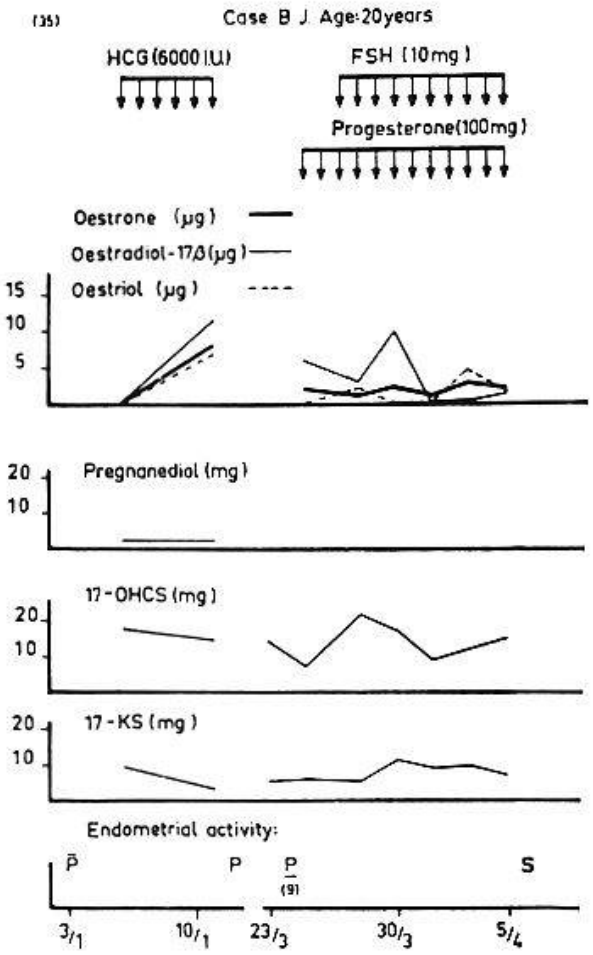


Fig. 10. Steroid excretion (48 h) and endometrial activity in a woman with secondary amenorrhoea during treatment with HP-FSH and progesterone (GEMZELL et al., 1960).

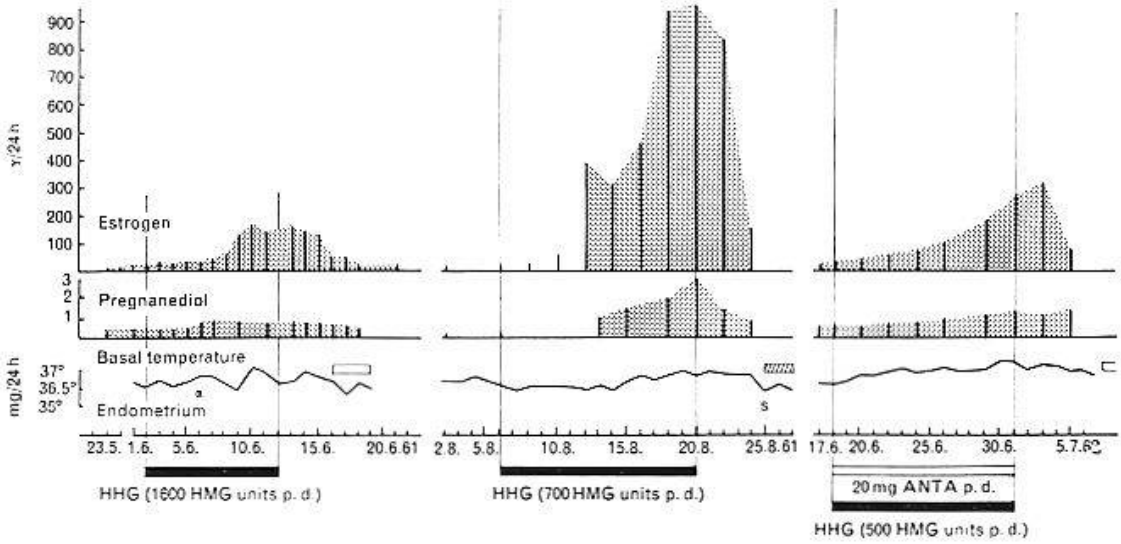


Fig. 11. Excretion of estrogens and pregnanediol in a hypophysectomized woman during therapy with HHG (endometrium: a = atrophic, s = secretory transformation, ANTA = aethinylnortestosteronacetate) (BETTENDORF, 1963).

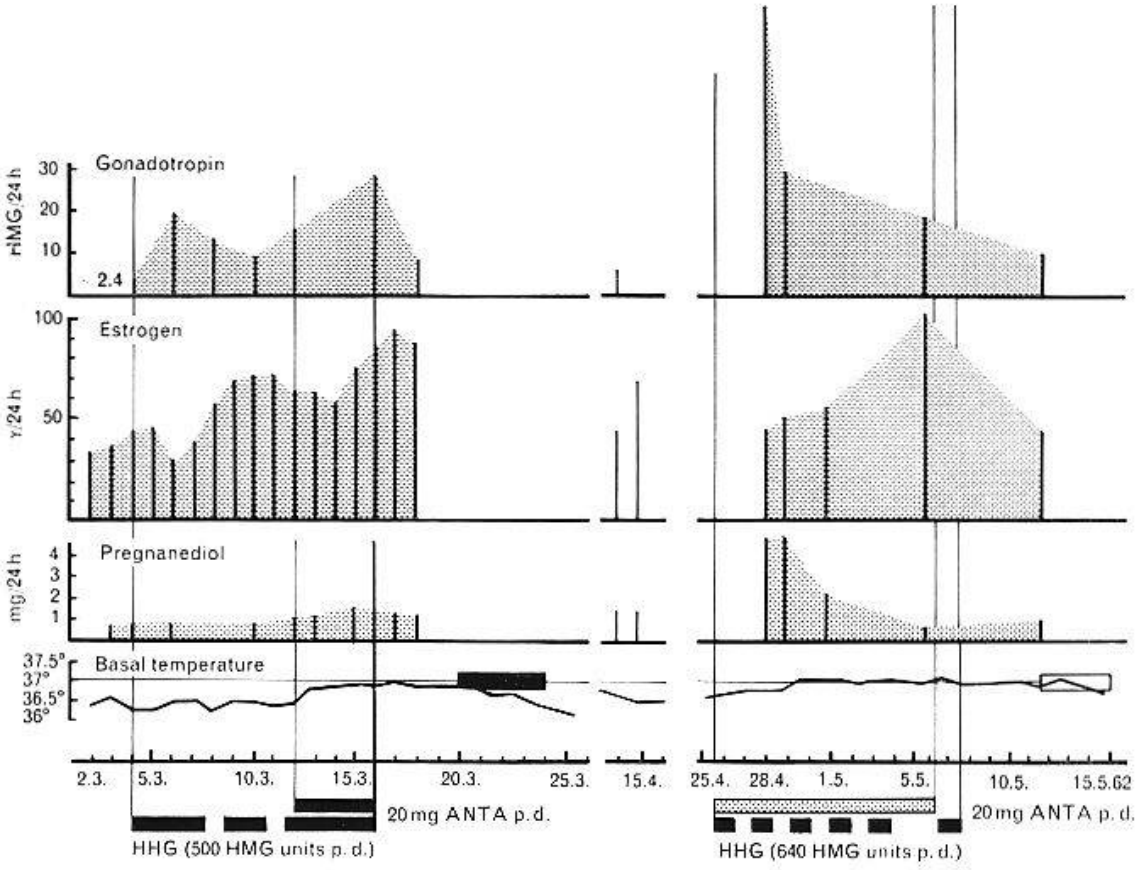


Fig. 12. Excretion of gonadotropin, estrogen, and pregnanediol in a patient with hypogonadotropic ovarian insufficiency (BETTENDORF, 1963).

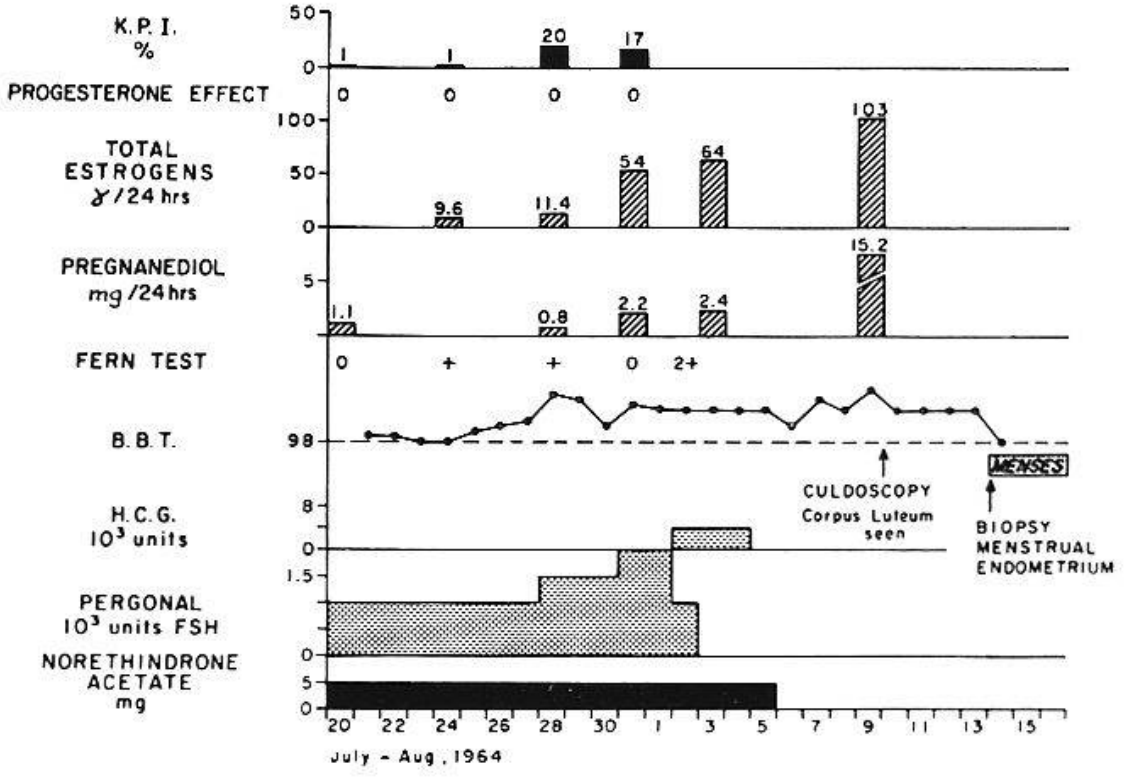
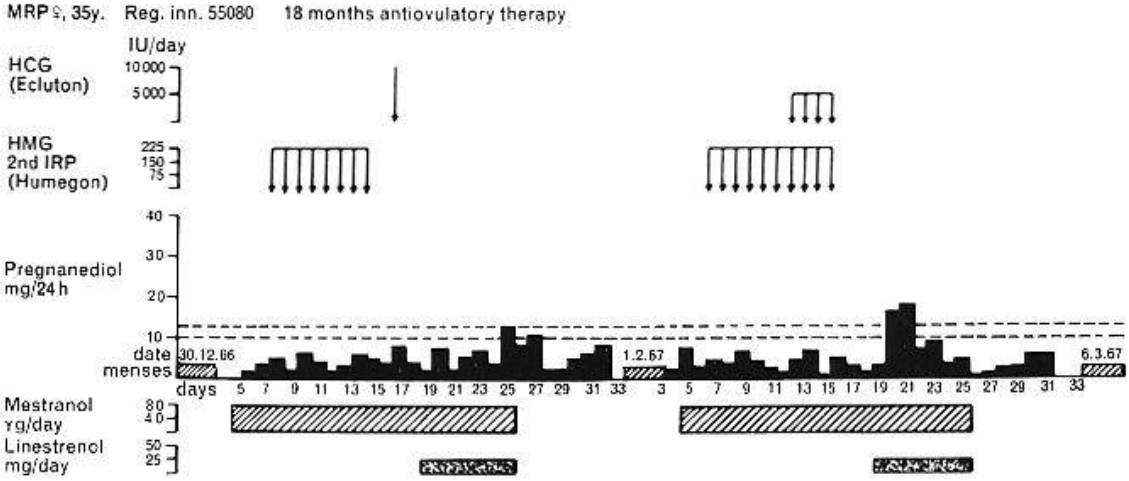


Fig. 13. Cycle 3. Norethindrone acetate, 5 mg daily, has been administered in addition to Pergonal and HCG (TAYMOR et al., 1965).



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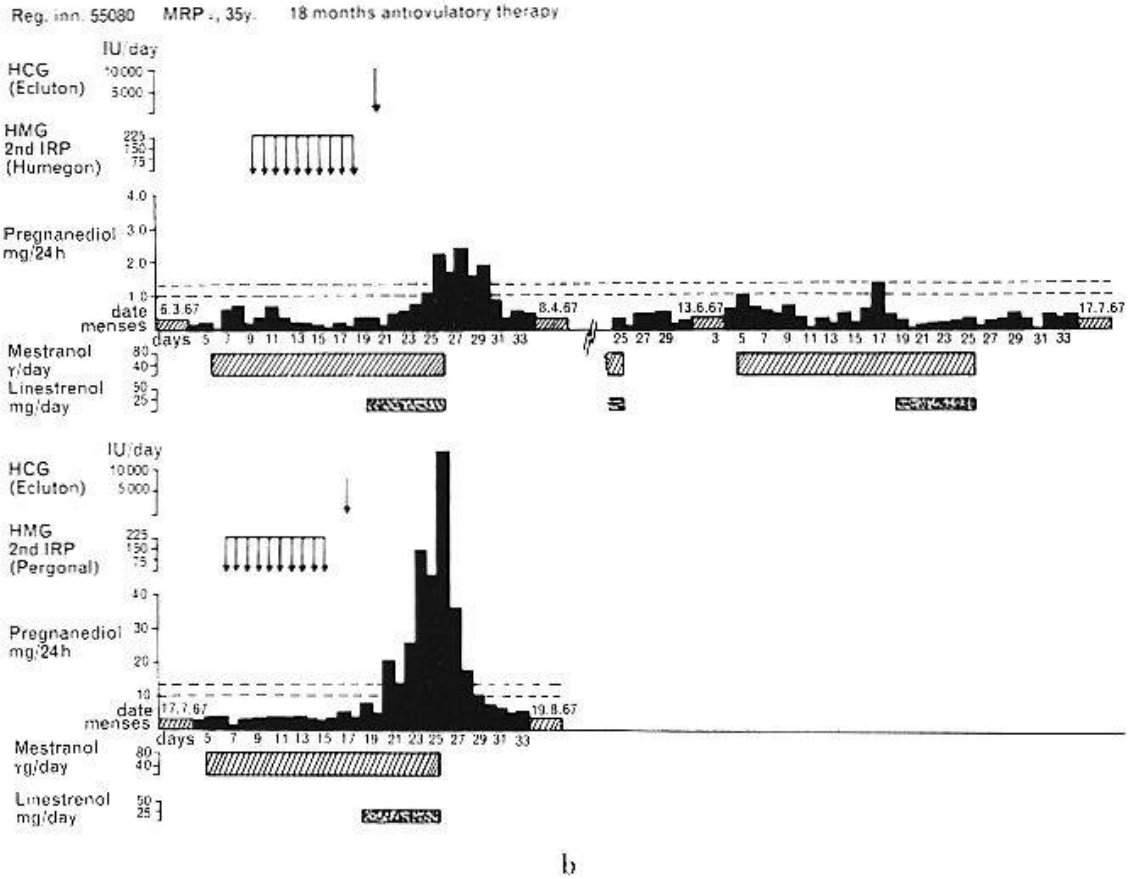

b

Fig. 14. – a) Ovarian response to exogenous gonadotropins in a normal patient under sequential antiovulatory therapy. – b) Ovarian response to exogenous gonadotropins in a normal patient under sequential antiovulatory therapy (Gual et al., 1968).

2. experimental studies of the influence of progestins on gonadotropin excretion and 3. the influence on exogenous gonadotropins in female patients. The clinical studies can give no answer on the site of action, although one would like to make an influence on gonadotropin release responsible for these effects, perhaps particularly on LH release. The results of the excretion studies are not uniform. This may be partly for technical reasons, but there is good evidence for a positive effect of progestins on gonadotropin release. Most interesting in this respect are the experiments of ODELL in postmenopausal women, in which it was possible to mimic the midcycle LH and FSH peak of an ovulatory cycle. In the studies of the effect of progestin on exogenous gonadotropin many sites of actions may have been involved. Different steroids in various doses were used, and the endocrine status of the patients was not the same.

Conclusions

It is obvious that gonadotropin secretion can be enhanced or inhibit in different species as well as in the human by progestins. From the studies done in this field one can only suggest that there is a regulating mechanism of progestins on gonadotropin function. Further studies must be done to find the exact site of action of these steroids on gonadotropin production and release as well as on gonadotropin action in the target organ.

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