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# CONTRACEPTION BY INTRAUTERINE RELEASE OF PROGESTERONE* CLINICAL RESULTS

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The need for taking the family planning programs to population groups who up to now had been completely unaware of the existence of contraceptive methods, has brought about an unforseen problem —women's failure to follow these methods.

Results obtained in research centers attended by women—whether these are motivated or have to be motivated by the investigator—frequently differ from those attained in the family planning clinics.

An example of this can be found in the hormonal oral contraceptives which are, unquestionably, the most effective of all methods and the ones that give the lowest continuation rate in the family planning clinics. In Mexico, among the socio-economic class served in these clinics, 60% of women abandon this method after the first year of use and 72% after the second year and, as a result, they find themselves in a very disadvantageous position, completely unprotected after deserting the method. (Correu, 1974).

A more practical alternative for mass programs is the use of improved intrauterine devices which may allow continuation rates higher than those observed with the conventional systems.

In view of the above, three years ago we thought it would be very interesting to initiate studies with hormonal intrauterine contraceptive systems which could combine the high efficacy of the steroids with a more practical method of administration, by having the hormone released within the uterine cavity, thus avoiding the constant motivation which is necessary with the use of oral contraceptives and the resulting systemic effects. (Martinez-Manautou *et al.*, 1974).

Scommegna's preliminary studies (1972) showing that the local effect of progesterone upon the uterus might reduce the incidence of expulsion and bleeding provoked by the inert devices and his initial observations regarding the possibility of increasing their contraceptive efficacy led to a remarkable bioengineering work undertaken by Alza Corporation in the U.S. They made available to us intrauterine systems which, utilizing Tatum's "T" shaped device as a platform for the delivery module, released various doses of progesterone, the natural hormone, at a precise and constant rate, during a year.

It is important that the System's contraceptive effect depends primarily on the hormone released rather than on a conventional IUD effect of the platform. This means that the platform can be designed, not specifically for contraception, but for maximum retention and patient comfort. The T configuration was chosen on the basis of studies described by Tatum (1972) which indicated the high rate of retention of the T, and its superiority to other IUD's in minimizing bleeding and pain. The platform itself does not provide effective contraception. Thus, though the Progesterone System is akin to IUD's by virtue of its intrauterine placement, it differs basically from the IUD's in a functional sense. It is, in essence, a method of steroidal contraception that localizes the effects of the hormone (Zaffaroni, 1974).

The Progesterone Uterine Therapeutic System (Fig. 1) is a T-shaped platform consisting of a rate-controlling ethylene/vinyl acetate copolymer membrane which encloses a reservoir of progesterone (38 mg), silicone oil, and barium sulfate. Dimensions are 32 mm for the crossbar of the T and 36 mm for its vertical stem. The top center of the latter has a ball-like extension that rises 1·5 mm above the crossbar,

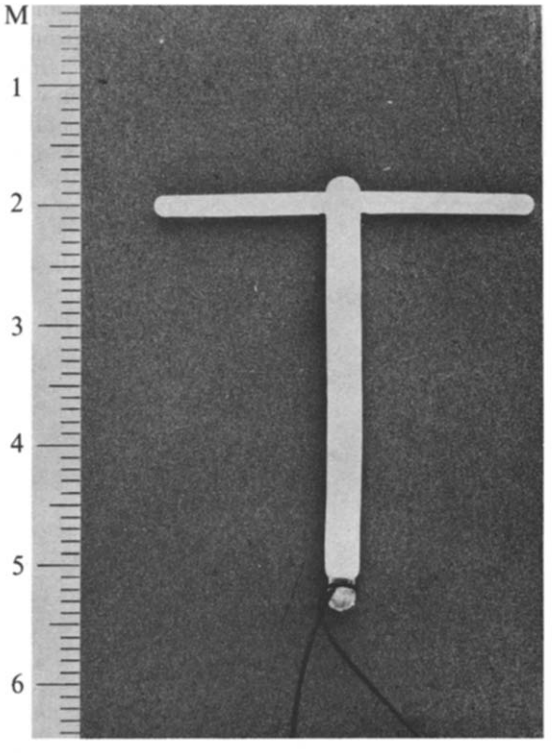


Fig. 1.

* Progesterone Systems for this study provided by Alza Corporation, Palo Alto, California, U.S.A. and Alza Mexicana, México, D. F.

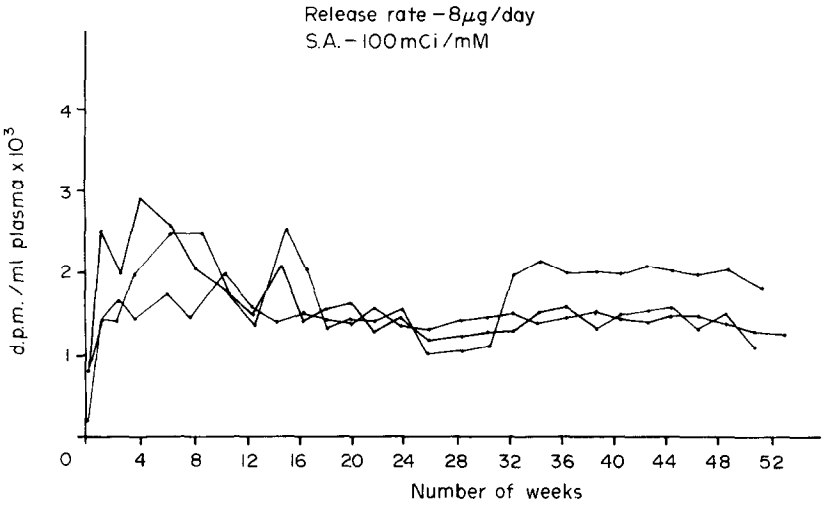


Fig. 2. Appearance of $^{3}H$ in plasma following intrauterine placement of $^{3}H$-progesterone system.

facilitating placement in the cervical os prior to insertion, particularly in women with small cervices. Attached to the bottom of the T are two threads. The longer one retains the system in its inserter before placement. The shorter thread extends 9 cm. from the top of the T and is used to ascertain its correct positioning. The physician can measure the length of the shorter thread extending from the cervix when the system is in place. Softness is engineered into the vertical portion of the T to prevent downward penetration into cervical tissue.

The System is packaged sterile in its inserter. The inserter, developed in the ALZA laboratories, is designed as a single curved tube, much like a sound. The absence of a plunger minimizes the possibility of uterine perforation during insertion. The horizontal arms of the T are positioned outside of the inserter and are folded downward just prior to insertion with an arm-cocker attachment. The inserter is calibrated to read from the base of the arm-cocker at 5, 6, 7, 8, 9 and 10 cm. to indicate depth of insertion.

It has been confirmed that the *in vitro* release behaviour of progesterone is consistent with that expected of a membrane-controlled process. By measuring the progesterone diffusivity and solubility in the polymer, it has been estimated that the System should release progesterone at a pre-programmed rate. This theoretically agrees with measured *in vitro* and *in vivo* release rates.

In vivo (*Rhesus monkeys and humans*)

The first quantitative measures of *in vivo* functionality of the progesterone uterine therapeutic system were undertaken in rhesus monkeys. The purpose was to investigate the release rates of $^{3}H$-progesterone in two types of polymeric systems. Small scale prototypes of the present system were fabricated incorporating radioactively-labeled hormone (Kulkarni *et al.*, 1973).

Systems designed to release either 8 μg or 100 μg of progesterone/24 h were surgically placed in the uteri of the monkeys. Blood and urine were obtained

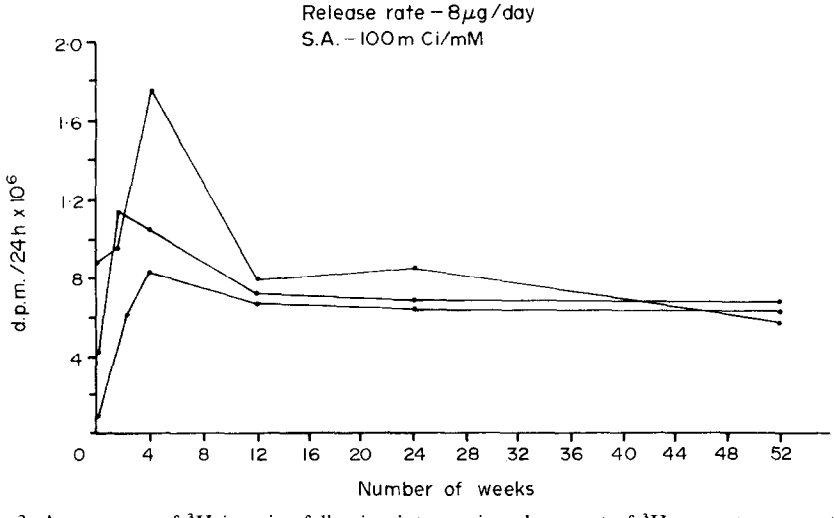


Fig. 3. Appearance of $^{3}H$ in urine following intrauterine placement of $^{3}H$-progesterone system.

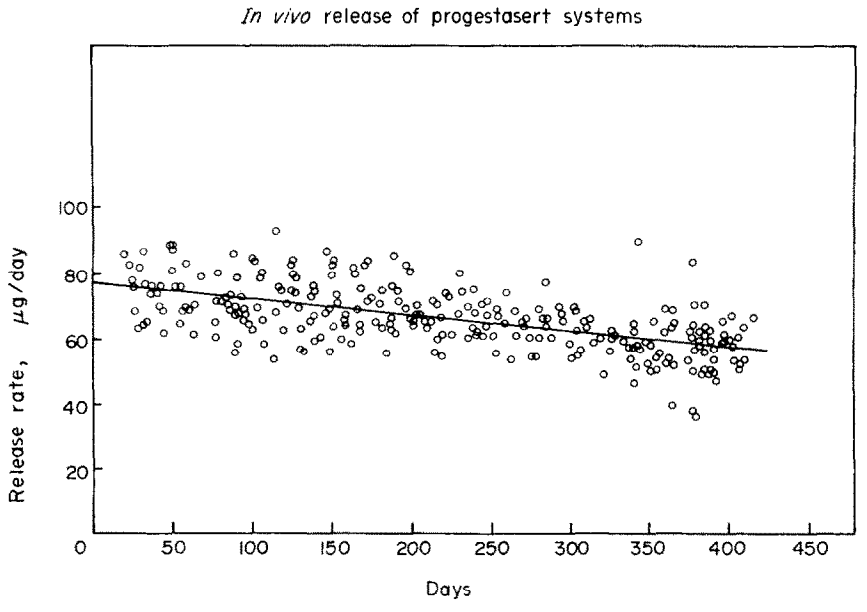


Fig. 4.

from each monkey at regular intervals for one year, and radioactivity in the plasma and urine was measured. (Figs. 2 and 3).

Initially there were fluctuations, especially in the high dose systems, due to uptake and distribution of the radioactivity. Essentially steady state levels were attained between 12 and 24 weeks, and persisted for the remainder of the experiments.

For the Progestasert or Systems releasing 65 μg of progesterone a day that have been *in utero* in humans for various periods, the release rate is essentially constant and identical to the *in vitro* value. (Fig. 4). The data were drawn from detailed chemical and physical analyses made of many Systems returned from the clinic after varying periods of patient use.

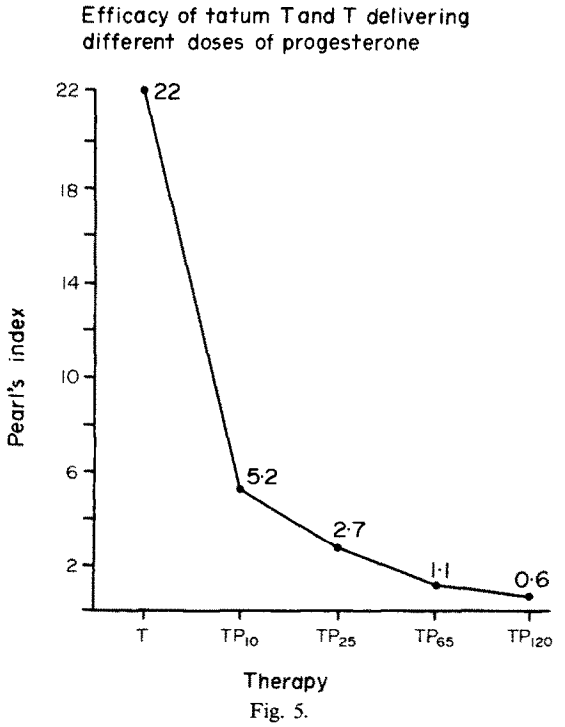


Fig. 5.

Accordingly, our studies have been directed, for the last three years to: (1) Evaluate the clinical performance of these systems; (2) Study the endometrial morphological and biochemical changes provoked by the local action of the progesterone; (3) Determine the effect, if any, of the progesterone locally released upon the hypothalamic-hypophyseal-ovarian axis.

As for the System's clinical performance, as can be observed in Fig. 5, we have tabulated both the results obtained with the empty platform and with the platform containing the delivery module and programmed to release 10, 25, 65 and 120 μg/day of progesterone. All devices used for this study were of identical dimensions.

Aside from the results obtained with the release rate of 10 μg of progesterone (TP-10), we have already completed a one year study with the release rates of 25, 65 and 120 μg/day. In the studies performed with the empty T the efficacy index obtained was 22, which was similar to the one reported previously by Tatum and Zipper (1969) of 18·3.

It is interesting to observe that even in preliminary studies when hormonal systems releasing 10 μg/day of progesterone are used, the efficacy index improves considerably—5·2 up to this date. When the dose of progesterone released is a little higher (25 μg/day), the efficacy obtained in 1-yr studies has been 2·7.

The system with which we have acquired wider experience is the one delivering 65 μg/day; the efficacy index obtained with this release rate is 1·1. This system has been studied not only in Mexico and the U.S. but also in 30 Research Centers throughout the world; results of this cooperative trial are shown on Tables 1 and 2.

The system releasing 120 μg/day of progesterone, which has been tried by our group in Mexico, has given thus far an index of 0·6.

Table 1. Life table analysis of event rates with the progestasert-65 system in parous women (time covered—one year)

| | Rate | ± | SE* |
|---|---|---|---|
| Pregnancy | 1.0 | ± | 1.2 |
| Expulsion | 2.8 | ± | 0.3 |
| Removal: | | | |
| Pain Bleeding | 8.2 | ± | 0.6 |
| Other Medical Reasons | 2.3 | | |
| Planned Pregnancy | 1.2 | | |
| Other non-medical reasons | 1.3 | | |
| Total - Termination | 16.8 | | |
| Continuation | 83.2 | ± | 0.8 |

* SE - Standard Error

Based on 3121 insertions - 25,389 woman-months - new inserter.

It is evident, according to these studies, that the highest contraceptive efficacy is given by the hormonal systems and not by the platform utilized to release the progesterone *in utero*. Apparently, there is a correlation between dose and contraceptive effect; the higher the dose released the greater the effect. However, it is necessary to extend the studies with the lower and higher doses of 10 and 120 μg/day to other centers, in order to confirm the above assumption.

As regards the clinical performance of these systems upon other parameters such as length of cycles, intermenstrual bleeding, expulsion and removal for different reasons, it is our impression that all of them behave alike.

For instance, the percentage of length of menstural cycles between 25 and 35 days varied from 72 to 78% with the different delivery systems. The incidence of amenorrhea ran from 0·9 with the dose of 10 μg/day to 1·5 with the 120 μg/day release rate. The incidence of intermenstrual bleeding is also similar with all the systems we have studied, having observed that with the dose of 10 μg/day this incidence is higher during the first 2 months and thenceforth lesser than that observed with the other systems. Another finding worth mentioning is that with the daily dose of 120 μg most of the bleeding informed occurred in the form of spotting.

As far as expulsion and removal are concerned, the incidence was practically the same with all the systems studied.

In order to observe the morphological changes provoked by these systems on the endometrium, a blind study was carried out in 402 endometrial biopsies of women users of intrauterine devices releasing different daily amounts of progesterone. 175 of these biopsies were obtained in what presumably was the proliferative phase and 227 in the secretory stage.

With all dose levels of the progesterone releasing devices there was a variation in the endometrium general pattern, and the overall picture changed from normal secretory to suppressed endometrium.

In addition to these changes in the endometrial pattern, in 231 specimens there was significant inflammatory infiltration and in 6 cases even plasma cells were seen. Predecidual reaction was frequently seen and, in 45 cases, this was diffuse and marked. (Martínez-Manautou *et al.*, 1974).

The changes observed are, in general, similar to those reported in women taking combined oral steroids for contraception. This similarity called our attention to the participation of endometrial changes in the mechanisms of the contraceptive action of these systems.

The studies carried out by Rosado *et al.* (1974), also suggest the importance of the endometrial biochemical changes in this mechanism of action. Uterine washings obtained from Progestasert wearing women produce a significant decrease in oxygen uptake and glucose utilization, an inhibition of the BANA-hydrolytic activity, and changes in the tetra-

Table 2. Life table analysis of event rates with the progestasert-65 system in parous women (2nd yr—8 months)

| | Rate | ± | SE* |
|---|---|---|---|
| Pregnancy | 0.8 | ± | 0.6 |
| Expulsion | 1.4 | ± | 0.7 |
| Removal: | | | |
| Pain, Bleeding | 2.6 | ± | 0.9 |
| Other Medical Reasons | 1.4 | | |
| Planned Pregnancy | 2.2 | | |
| Other non-medical Reasons | 0.5 | | |
| Total - Termination | 8.9 | | |
| Continuation | 91.1 | | |

* Standard Error

Based on 385 insertions - 1,995 woman-months - new inserter

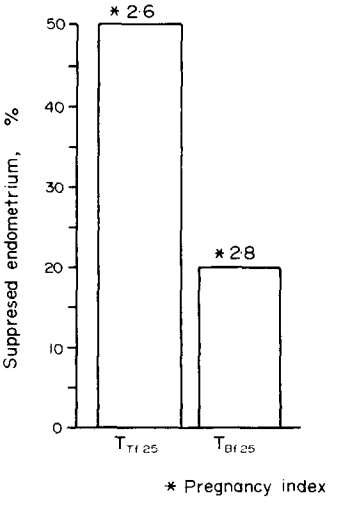


Fig. 6.

cycline binding and release processes. All these changes support the hypothesis that at least part of the mechanism of action of the progesterone-releasing type of intrauterine devices is due to a direct capacitation inhibiting effect of the uterine secretion. This hypothesis is strengthened by the direct demonstration of inhibition of *in vitro* rabbit spermatoza capacitation produced by these washings.

Hicks *et al.* (1974), carried out a study on the biochemical composition of human endometrial biopsies obtained in the proliferative ($10 \pm 1$ days) and secretory ($20 \pm 1$ days) phases, from a group of 40 fertile women, between 20 and 30 yr of age, who were not receiving any contraceptive treatment (control group). Another study was performed with a second group of 40 women wearing devices releasing 10, 65 and 120 $\mu$g/day of progesterone (P-10, P-65 and P-120). Ten patients were studied with the device releasing 10 $\mu$g/day of progesterone, 20 with the one delivering 65 $\mu$g and ten more with the 120 $\mu$g/day unit.

In the proliferative phase, when comparing the control group with the P-10, P-65 and P-120 groups, the three last ones presented a significant reduction ($P$ 0·001) in the concentration of fucose + (0·573 to 0·160), sialic acid + (0·054 to 0·021), fucose/sialic acid ratio (11·78 to 7·2), $Zn^+$ (0·03 to 0·001) and $Ca^+$ (0·049 to 0·03) and an increase in the concentrations of Na (0·05 to 0·256) and K (0·04 to 0·23); the concentrations of Mg remained unchanged. In the secretory phase a reduction was observed in the concentrations of fucose (0·32 to 0·13), sialic acid (0·028 to 0·015), fucose/sialic acid (11·78 to 7·54), while the Mg, Na and K were increased; no change was observed in the Zn determinations. There were no differences among the P-10, P-65 and P-120 groups in neither phase. The quantification of proteins, DNA, RNA and total hexoses did not present modifications statistically significant in the groups studied.

A study was performed of the utilization of glucose by the human endometrium (U-$C^{14}$) in a system of radiorespirometry, in which the production of $C^{14}O_2$ and of lactate $C^{14}$ to proteins and lipids in the proliferative and secretory phases of the cycle, were determined.

In the proliferative phase the progesterone releasing systems provoked a lessening in the production of lactate $C^{14}$ (133 to 53) and in the incorporation of $C^{14}$ to proteins (65 to 27) and lipids (267 to 98). In the secretory phase no changes statistically significant occurred between the groups P-10, P-65, P-120 and the control group.

The frequency of cases of suppressed endometria is a participating factor but not the only one, to explain the high contraceptive efficacy of these systems.

This is illustrated by the study we carried out with two types of delivery modules (Fig. 6); in one of them the progesterone (25 $\mu$g/day) was released from the upper half of the vertical section of the "T" and, in the other, the release took place from the lower half of this section.

The incidence of suppressed endometria in the first group was approximately 50% and only 20% in the second group. If these endometrial changes were of primary importance to explain the contraceptive efficacy of these systems, this efficacy should have been higher in the group releasing the progesterone from the upper half of the "T"; however, results in both groups were practically the same, and this indicates the participation of other factors aside from the morphological and biochemical endometrial changes.

To determine the effect of the progesterone locally released upon the hypothalamo-hypophysial-ovarian axis, luteinizing hormone, follicle stimulating hormone, estradiol and progesterone were measured in blood plasma of women wearing either a Progestasert System releasing 65 $\mu$g of progesterone a day or an identical but non-hormone releasing unit during one menstrual cycle. No significant differences in hormone levels were found between the two groups of women. Overall cycle lengths were comparable in the two groups although the secretory phase of Progestasert wearers appeared to be somewhat longer. No statistical differences were shown. It was concluded that women wearing the Progestasert System showed no alteration in the pituitary-ovarian axis or in menstrual cycle periodicity. (Tillson *et al.*, 1974). (Fig. 7).

The mechanisms of contraceptive action of progesterone applied directly to the uterine lumen have not been established. It is clear, however, that the mechanisms differ from those of oral contraceptives, which affect the hypothalamic-pituitary-ovarian axis.

Our conclusion, at this point, is that with two of the progesterone releasing systems designed for this investigation, those delivering 65 and 120 $\mu$g/day during a year, efficacy levels can be reached similar to those obtained with the most effective hormonal methods. The advantage over these methods resides in the fact that the progesterone releasing systems do not provoke systemic hormonal side effects and that minimum motivation is required for its use.

During the first-year study with the system releasing 65 $\mu$g/day the continuation rate obtained in Mexico was 89 which is superior, by far, to the one informed, also in Mexico, for the conventional contraceptive pill which was 40.

It is worth mentioning that a group of 150 women are about to finish the second year of use with the 65 $\mu$g/day system, with even better results than those obtained during the first year. The incidence of bleeding decreased drastically and no pregnancies nor expulsions have occurred. Our conclusion is that the woman who tolerates this system the first year can better accept it during the second one.

Considering that these hormonal systems do not provoke systemic side effects, we believe that studies should be furthered in order to obtain systems that might release the natural hormone, progesterone, for over a year and take advantage of this important research in the field of bio-membranes to develop other controlled hormone-releasing methods for contraception.

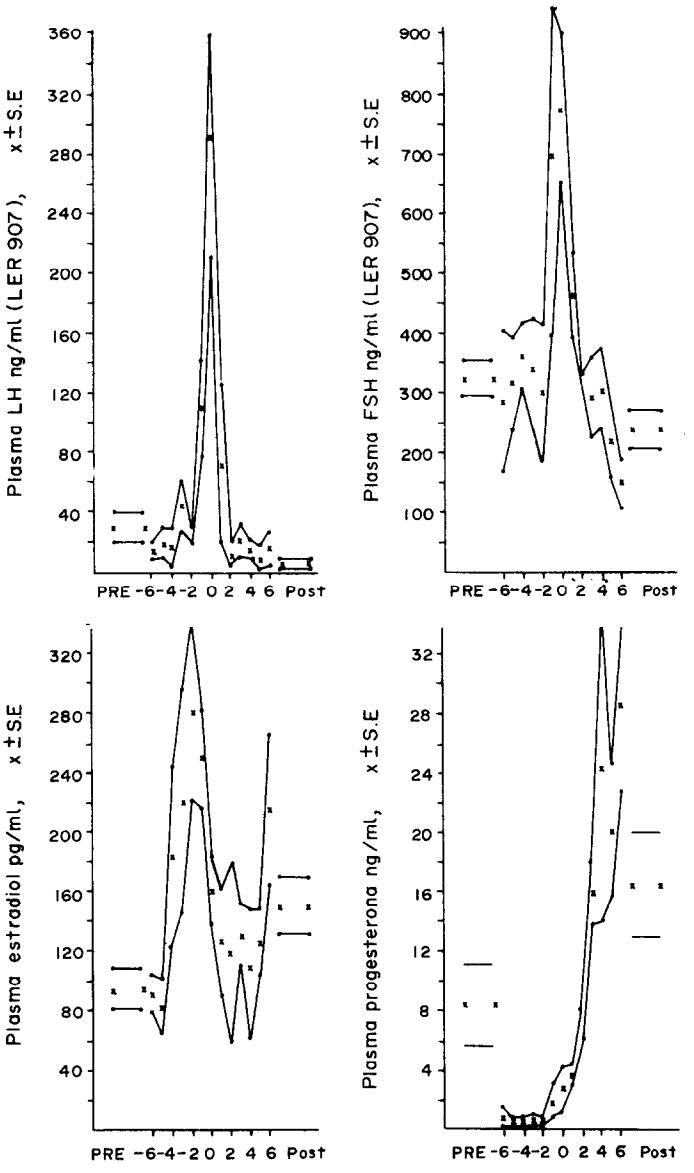


Fig. 7.

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