BRIEF COMMUNICATION

INHIBITION OF FERTILITY IN RATS AND HAMSTERS BY STEROID IMPLANTS

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Summary. We have recently reported that 19-norprogesterone pellets implanted into adult mice inhibit fertility (Folch Pi, Oriol, Herrera Lasso, Maqueo, Dorfman & Kincl, 1965). The amount of the active substance, released from the steroid-cholesterol preparation was shown to be about 10 $\mu\text{g/day}$. Such low amounts were apparently not sufficient to inhibit hypothalamo-hypophysial function and fertility control was achieved by other mechanisms.

The present studies were undertaken with the purpose of establishing whether similar control of fertility could be achieved in rats and hamsters by pellet implants.

The rats used were either Wistar or Sprague-Dawley strain. Circular, flat pellets (6×1.1 mm) weighing about 30 mg were implanted at separate sites in the dorsal region during pro-oestrus. Control animals were either sham-operated, or were implanted with cholesterol pellets. Two days after implantation each female was caged with two males and allowed to remain for 20 days. The females were removed and allowed to deliver their young at which time the females and young were killed and autopsied; the young were counted and weighed and the sex was determined. Non-pregnant females were autopsied 10 days after all pregnant rats had delivered their young. Adult female ovaries were weighed and corpora lutea were counted, uteri were examined for implantation and resorption sites. Hamsters were treated in a similar way to the rats.

Inhibition of fertility in rats with one to four implanted pellets of varying concentration of 19-norprogesterone is shown in Table 1.

Females implanted with pellets containing 20% of 19-norprogesterone and 80% cholesterol were all infertile, due apparently to inhibition of pituitary function. The ovaries were small and usually contained only few small and growing follicles. Only in the last group were there five of seven animals which had ovaries with corpora lutea. These, however, were small and few in number. In addition, females implanted with four 10% pellets had atrophied ovaries containing small, regressing corpora lutea. No implantation sites were noted

in the uteri of these groups. In a few cases resorption scars were noticed in these two groups. When only two 10% pellets were used an average of 3.4 ± 2.3 (S.E.) normally developed young were born to the treated females as compared with 12.0 ± 0.3 pups born to controls. The ovaries contained a number of well-developed corpora lutea and the average weight was greater than that of the controls.

Lower amounts of 19-norprogesterone inhibited neither fertility nor ovulation.

TABLE 1
INHIBITION OF FERTILITY IN ADULT FEMALE RATS BY 19-NORPROGESTERONE (NP) IMPLANTS

Percent. NP /pellet	No. of pellets	Total No. of rats used	Average No. of uterine implan- tation sites $\pm$ S.E.	Average No. of corpora lutea $\pm$ S.E.	Ovarian weight $\pm$ S.E. (mg)
0	0	17	12.0 ± 0.3	13.6 ± 0.6	74.8 ± 5.5
Cholesterol	4	6	12.2 ± 0.7	13.7 ± 1.2	114.0 ± 6.3
20	4	6	0.0 ± 0.0	0.0 ± 0.0	38.2 ± 1.1
	2	6	0.0 ± 0.0	0.0 ± 0.0	34.4 ± 1.1
	1	6	0.0 ± 0.0	Several*	41.5 ± 5.2
10	4	12	0.0 ± 0.0	> 15.0	65.0 ± 2.1
	2	10	3.4 ± 2.3	> 15.0	106.0 ± 7.4
	1	10	8.6 ± 1.8	13.6 ± 0.7	106.0 ± 5.8
5	1	5	8.6 ± 1.7	> 15.0	106.0 ± 4.5
1	1	6	9.5 ± 0.7	12.3 ± 0.8	90.7 ± 6.1

* Involuting corpora lutea.

TABLE 2
INHIBITION OF FERTILITY IN ADULT FEMALE HAMSTERS
BY 20% 19-NORPROGESTERONE IMPLANTS

No. of pellets	No. of animals	Average No. of uterine implan- tation sites $\pm$ S.E.	Average No. of CL $\pm$ S.E.	Ovarian weight S.E. $\pm$ (mg)
0	6	10.7 ± 0.3	11.3 ± 0.4	44.4 ± 2.0
4	6	0.0 ± 0.0	9.0 ± 1.0	21.6 ± 3.2
2	6	0.0 ± 0.0	8.0 ± 0.6	23.6 ± 2.5
1	6	0.0 ± 0.0	8.2 ± 1.1	19.1 ± 1.8

In one experiment ten females were implanted with one 20% pellet for 30 days. In seven animals fertility was inhibited during the test period. Upon removal of the pellet fecundity returned within the average period of 23 days (range from 9 to 40 days). The number of offspring born was within normal limits.

The antifertility effect of 19-norprogesterone in hamsters was studied using three different concentrations (Table 2). In all groups the average number of

observed corpora lutea was comparable to controls, but no young were born and no implantation sites were seen in any of the uteri at autopsy.

Neither rats nor hamsters have shown any other adverse effects attributable to the treatment. The average body weights showed no significant variations. Offspring born to females in the treated groups were well developed and showed no signs of malformation.

Our present data show that, in the rat, infertility induced by 19-norprogesterone implants was in most cases due to inhibition of hypothalamohypophysial function. This is supported by the observed ovarian atrophy and lack of corpora lutea formation. The presence of only few growing follicles may further indicate that the treatment interfered not only with the secretion of the luteinizing hormone but possibly also with that of follicle-stimulating hormone. There was only a narrow therapeutic range at which fertility was partially inhibited in the presence of unimpaired ovarian performance.

In the hamster 19-norprogesterone caused infertility but did not prevent the formation of corpora lutea. These effects resembled the response seen previously in mice (Folch Pi *et al.*, 1965).

This method, especially if mice or hamsters are used, may be suitable for testing new compounds for blocking human fertility but not ovulation (Martinez-Manautou, Cortez, Giner, Aznar, Casasula & Rudel, 1966).

REFERENCES

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