THE CONTRACEPTIVE ACTION OF IMPEDING OESTROGENS

VI. CONTRACEPTIVE ACTIVITY OF OESTRIOL DERIVATIVES

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Previous publications from this laboratory (Wotiz & Scublinsky, 1971; Scublinsky & Wotiz, 1971) have shown that oral administration of oestriol *post coitum* (*p.c.*) resulted in prevention of implantation of blastocysts at doses of 0.25 mg/day. Similarly, an analogue of oestriol, 18-homo-oestriol, prevented conception in oral doses of 1 mg or more. It is reasonable to consider that the dose of steroid required for prevention of implantation may depend on the rate of its metabolic removal and on its solubility in adipose tissue for storage, among other factors. Thus, triesters of oestriol, which can be stored more readily by virtue of their greater solubility, i.e. lipophylic character, and are also capable of being hydrolysed *in vivo*, might exhibit activity at lower concentrations.

Four groups each of four Sprague-Dawley rats (250 g) were mated during pro-oestrus. Mating was checked by observation of spermatozoa in the vaginal smear. Following mating, the animals were anaesthetized with ether and given an oral infusion of (a) 1 ml of sesame oil, (b) 0.15 mg of oestriol (0.52 μ mol) in sesame oil, (c) 0.263 mg of oestriol tripropionate (0.52 μ mol) in sesame oil, and (d) 0.216 mg of oestriol triacetate (0.52 μ mol) in sesame oil, daily for 4 days.

On the 10th day following proven mating, the animals were killed, the uteri removed and the number of implantation sites recorded.

The results obtained are shown in Table 1. As expected, all the control animals became pregnant with an implantation density of 7.25/horn. Oestriol does not become completely effective as a contraceptive until 0.25 mg/day (Scublinsky & Wotiz, 1971) of this steroid is administered. Thus, after administration of only 0.15 mg of oestriol, all animals showed implantations though in each instance, markedly fewer sites were observed. The tripropionate of oestriol appeared to be essentially ineffective as a contraceptive, possibly through lack of specific hydrolytic enzymes in the rat precluding adequate formation of free oestriol to act on the endometrium. Oestriol triacetate, on the other hand, was significantly more effective as an oral contraceptive *p.c.* as shown by the fact that three out of four animals did not become pregnant and the single pregnant rat showed fewer than the normal number of implantations, all of which were confined to a single uterine horn.

This might have been due to longer retention of oestriol in the animal, and to release of free steroid through mediation of endogenous acetylases.

In summary, it appears that use of a hydrolysable derivative of oestriol allows reduction of the required dose for effective control of blastocyst implantation in the rat.

TABLE 1
EFFECT OF OESTRIOL AND ITS ESTERS ON IMPLANTATION

Group	No. of implants/rat				Average no. of implants
	Rat 1	Rat 2	Rat 3	Rat 4	
Control	7.5	8	6.5	7	7.25
Oestriol*	2	3	2	1	2.0
Oestriol tripropionate*	7	7	2	9	6.25
Oestriol triacetate*	0	0	0	3†	0.75

* Each animal received the equivalent of 0.52 μ mol oestriol orally for 4 days.

† All three implants were in the same uterine horn.

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