

Ergocryptine and Pregnancy Maintenance in Hamsters¹ (9049)J. J. FORD² AND K. YOSHINAGA*Laboratory of Human Reproduction and Reproductive Biology and Department of Anatomy, Harvard Medical School, Boston, Massachusetts 02115*

Placentae of rats produce a luteotrophic hormone which can maintain pregnancy in the absence of hypophyseal support after Day 11 of gestation (1-3). Stimulation of luteal activity in hypophysectomized pseudo-pregnant rats demonstrated that this hormone in placenta and serum of pregnant rats reached its maximal activity on Day 12 of gestation (4). Placental function in hamsters has not been investigated extensively; Madhwa Raj *et al.* (5) reported maintenance of pregnancy in six of nine hamsters after hypophysectomy on Day 12 indicating that hypophyseal support of luteal activity can be dispensed with at this time in some animals. Furthermore, after Day 9 of pregnancy peripheral progesterone reaches peak levels in hamsters and further growth of corpora lutea is initiated (6, 7). In contrast to hysterectomy between Days 8 and 13 of pregnancy which causes regression of corpora lutea, removal of fetuses leaving placentae intact results in maintenance of corpora lutea size (8). The results of these investigations suggest the presence of a hamster placental luteotrophin.

In the present study the effect of ergocryptine on pregnancy maintenance in hamsters was observed since ergocryptine is one of the ergot alkaloids which inhibit prolactin secretion. These drugs effectively suppress prolactin levels in all species investigated to date; rat (9), cow (10), goat (11), sheep (12) and human (13). The abortifacient effect of ergot alkaloids in rats gradually decreases (14, 15) because of a gradual increase in placental luteotrophin secretion (4, 16).

Materials and methods. Hamsters mated in our laboratory were maintained under a

lighting schedule of 14 hr light and 10 hr darkness and the day of sperm detection in the vaginal smear was designated Day 1 of pregnancy. Ergocryptine mesylate (ECR) (Sandoz Pharmaceuticals) was dissolved in 95% ethanol and diluted with distilled water to a final concentration of 2 mg ECR/ml of 20% ethanol. Pregnant hamsters were injected subcutaneously once with 1 mg ECR between 0900 and 1100 hr on a designated day of pregnancy. Nontreated pregnant animals were decapitated between 0900 and 1100 hr on different days of gestation and the sera from two to four hamsters pooled and stored at 4° using *n*-butanol as preservative (0.1 ml/25 ml of sera). These sera were tested for luteotrophic activity by administering them subcutaneously twice daily on Days 5 and 6 to pregnant hamsters which received 1 mg ECR on Day 5. Pregnancy maintenance in ECR treated animals was determined on Day 8 or 11 by examining uterine contents for viable fetuses. Ovine FSH, LH and prolactin were dissolved in saline and administered subcutaneously.

Results. Table I illustrates the effect of ECR on pregnancy maintenance in hamsters. No pregnancies were maintained when 1 mg ECR was given on Day 5; by Day 6 the abortifacient effect of ECR was diminished, and by Day 7 ECR was ineffective at interrupting pregnancy. When 0.5 mg of ECR was given instead of 1 mg the trends were similar except pregnancy continued to Day 11 in 2 of 7 animals treated on Day 5.

Prolactin at a daily dose of 300 µg on Days 5 and 6 of gestation reversed the effect of 1 mg of ECR on Day 5 in pregnant hamsters (Table II). FSH and LH were ineffective at the levels tested.

Pooled sera collected on various days of gestation were tested for their ability to maintain pregnancy in hamsters treated on Day 5 with 1 mg ECR (Fig. 1). Sera collected on Day 9 did not maintain pregnancy

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TABLE I. PREGNANCY MAINTENANCE IN HAMSTERS AFTER TREATMENT WITH ERGOCRYPTINE (ECR) ON DESIGNATED DAYS OF GESTATION.

Day of treatment ^a	Amount of ECR (mg)	No. pregnant on Day 11/No. treated
5	0.5	2/7
5	1.0	0/7
6	0.5	3/6
6	1.0	3/8
7	0.5	3/3
7	1.0	8/8
8	1.0	6/6

^a All animals were treated between 0900 and 1100 hr.

TABLE II. EFFECTIVENESS OF EXOGENOUS HORMONES AT OVERRIDING THE ABORTIFACIENT ACTION OF ERGOCRYPTINE IN DAY 5 PREGNANT HAMSTERS.^a

Hormone	Total daily dose ^b (μ g)	No. pregnant on Day 8 ^c /No. treated
Prolactin (NIH-S8)	100	0/3
	200	0/3
	300	6/8
	500	3/3
FSH (NIH-S9)	200	0/3
LH (NIH-S18)	50	0/3
	100	0/3

^a All animals were treated between 0900 and 1100 hr on day 5 of gestation with 1 mg of ergocryptine.

^b Daily dose was divided equally and administered subcutaneously, twice on days 5 and 6.

^c All nonpregnant hamsters had blood-filled uteri.

in ECR treated pregnant hamsters, but sera collected on Day 10 or 11 prevented interruption of pregnancy by ECR. The effectiveness of pregnancy sera collected after Day 11 diminished as gestation progressed. The effective dose of sera collected on Day 10 or 11 was 0.5 ml twice daily since the action of ECR was not overridden when sera collected on these days were each administered to two hamsters at a dose of 0.25 ml twice daily.

Discussion. The results of the present investigation demonstrate that ECR terminates pregnancy in hamsters when administered on Day 5 but is ineffective when given on Day 7. A similar response to ergocornine,

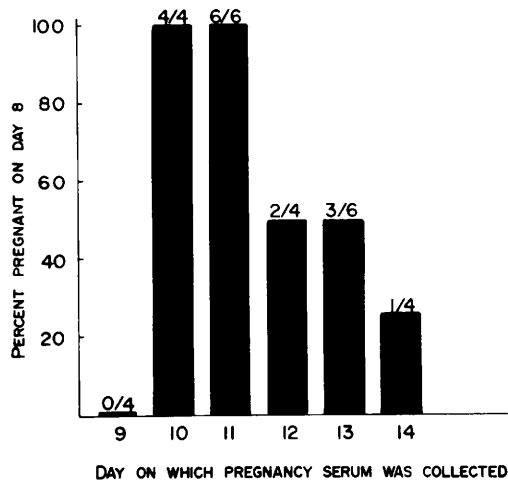


FIG. 1. Effect of pregnancy sera at maintaining gestation in Day 5 pregnant hamsters treated with 1 mg ergocryptine. Pooled sera were administered twice daily at a dose 0.5 ml on Days 5 and 6. Sera from a single pool were given to two test animals.

but delayed by 1 day, is observed in rats (14, 15) and is attributed to a diminished role of hypophyseal prolactin in luteal support which is replaced by an increasing role for placental luteotrophin. In hamsters hypophysectomized on Day 4, FSH and prolactin stimulate luteal progesterone secretion adequately to maintain pregnancy through Day 8 (17, 18); however, if hypophysectomy is performed on Day 8 hypophyseal prolactin is not needed and LH successfully maintains gestation to Day 12 (5). Moreover, the endocrine requirements for maintenance of pregnancy in the hamster further resemble the rat in that LH antisera terminates pregnancy when administered on Days 6 through 10 but its ability to terminate gestation is reduced after Day 10 (19). These findings combined with the observations of the current studies strongly suggest that in pregnant hamsters elevated hypophyseal prolactin secretion is not obligatory after day 6; and, as in the rat, the prolactin component of the luteotrophic complex (Days 7-11) may be replaced by a placental luteotrophin.

The abortifacient action of ECR in Day 5 pregnant hamsters was neutralized by exogenous prolactin or hamster pregnancy sera collected on Days 10 or 11 of gestation. The assumption that ECR specifically suppressed

prolactin secretion is supported by the ineffectiveness of FSH and LH at doses which are luteotrophic when combined with prolactin in hypophysectomized pregnant hamsters (5, 18). The ability of pregnancy sera to maintain gestation in ECR treated animals demonstrates the appearance of luteotrophic activity which is maximal on Days 10 and 11 of gestation. Since prolactin levels at this time are 50% lower than during early pregnancy (20), the luteotrophic activity in pregnancy sera is apparently not due to increased hypophyseal prolactin secretion. That the placenta is the probable origin of this material is supported by the report of Matthies (21) indicating luteotrophic activity in hamster placenta. Furthermore, the decline in luteotrophic activity of pregnancy sera as gestation progressed is similar to the situation in rats (4). Although the present data suggest the presence of a hamster placental luteotrophin, our initial efforts in using homogenates or extracts prepared from placentae collected on Days 10 and 11 of gestation have proved unsuccessful in maintaining pregnancy in ECR treated hamsters. It is not known whether this is due to a low concentration of hormone in placentae or to instability of the hormone during preparation.

Summary. Ergocryptine (ECR) terminated pregnancy in hamsters when administered on Day 5; when ECR was given on Day 6 the response was diminished, and pregnancy continued after ECR treatment on Day 7. The abortifacient action of ECR in Day 5 pregnant hamsters was overcome by exogenous prolactin but not FSH and LH. When sera collected from hamsters on different days of gestation were examined for their ability to neutralize the effect of ECR in Day 5 pregnant hamsters, a peak of luteotrophic activity was observed in sera collected on Days 10 and 11. The results of these studies suggest that in hamsters the role of hypophyseal prolactin in luteal support is diminished by Day 7 of pregnancy, and the appearance of luteotrophic activity

in sera collected on Days 10 and 11 may be indicative of a placental luteotrophin.

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