Luteolytic Effects of Prostaglandin $F_{2\alpha}$ in Primates[1] (34464)

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Very little is known of the specific factors which cause the demise of the corpus luteum. The uterus is apparently involved, since surgical removal of all or parts of the uterus during the luteal phase of a reproductive cycle or during pseudopregnancy prolongs the functional lifespan of the corpus luteum in many species (1). However, despite widespread investigations, the biological nature of this naturally occurring factor which is instrumental in causing the regression of the corpus luteum has not been determined. Recently a hypothesis for the mode of action of such a luteolytic factor was presented (2), in which one of the family of prostaglandins, $F_{2\alpha}$, seemed to fit. This prostaglandin is present in the uterine tissue, and possesses veno-constricting activity, two qualifications necessary for the hypothesis. Data obtained with pseudopregnant rats and rabbits supported the hypothesis (5, 6). Administration of PG-$F_{2\alpha}$ caused many of the physiological changes associated with normal regression of the corpus luteum, but at an earlier stage than would have been expected in normal untreated animals. The purpose of the present experiment was to determine if $F_{2\alpha}$ was luteolytic in rhesus monkeys.

Materials and Methods. Prostaglandin was injected as a suspension formed by dissolving PG-$F_{2\alpha}$ in 100% ethanol and combining with 0.25% methylcellulose in sterile water, 1:9 (v/v), to a concentration of 15 mg/ml. This suspension was injected subcutaneously b.i.d. at a dose of 30 mg/day for 5 consecutive days. All treated animals had been mated daily during the ovulatory phase of the menstrual cycle to maximize the incidence of conception. The experiment consisted of two replicates of three treated animals each in which injections were initiated on day 11, 12, or 13 postovulation. In two additional animals injection was initiated on day 4 or 7 postovulation. Injections in the former were continued for 7 days. Control animals were mated and serum progestin levels were compared with the treated animals. Signs of treatment efficacy were monitored by following circulating blood progestin levels, and the incidence of pregnancy.

A protein binding assay (3) was used to quantitate circuating progestin levels in peripheral plasma. Blood samples from the femoral vein were drawn into heparinized containers. Plasma was extracted twice with 3 vol of 30–60° petroleum ether, and the solvent was evaporated under N_2. Since this assay measures 17α-OH progesterone as well as progesterone in such plasma extracts the term progestin is used in this communication. The specificity, precision, and repeatability of the assay have been well established, and values obtained in our laboratory for these parameters agree with published results (3).

Results. Initially one animal was injected from day 7 through day 11 postovulation and three additional animals on days 11 through 15. Neither progestin levels nor menstrual cycle length were detectably altered by prostaglandin injection on days 7–11 postovulation, or by injection in a subsequent animal on days 4–10. However, progestin levels in the three animals injected on days 11–15 (Nos. 2, 13, and 21, Fig. 2) were depressed nearly to nondetectable levels and vaginal bleeding (menses) was initiated within 48 hr of the first drug injection. Progestin levels of one animal, No. 2, increased again on the fourth and fifth days of treatment and pregnancy was maintained.

Control animals simultaneously mated dis-

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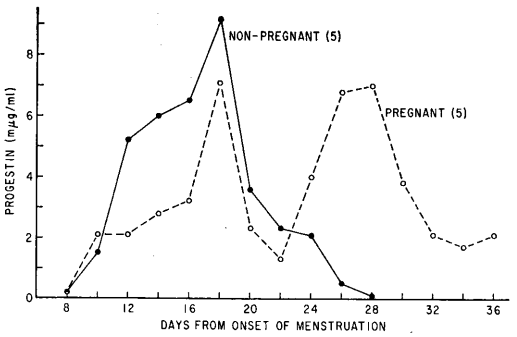

FIG. 1. Peripheral plasma progestin levels of pregnant and nonpregnant rhesus monkeys.

played a serum progestin pattern which indicated a pregnancy diagnosis could be made as early as days 11–13 postovulation. At this time, fertile animals are characterized by a rapidly increasing progestin level, in contrast to decreasing levels in nonpregnant animals (Fig. 1). Therefore, the three treated animals in the second replicate of the experiment (No. 7, 19, 525, Fig. 2) were injected only after the corpus luteum had received a second luteotrophic stimulus, presumably from the blastocyst, insuring the presence of a functional blastocyst at the initiation of treatment. In each of these three treated animals the trend of increasing blood progestin was reversed and levels were quickly (within 2 days) depressed nearly to nondetectable levels. Menses resulted within 2 or 3 days of the initiation of drug injection in each of these animals (Nos. 7, 19, and 525, Fig. 2). A fertility rate of one of six treated animals is compared to six fertile of 10 control matings. An even more striking difference between groups is the lack of an abrupt decline in blood progestin levels at this state of the fertile cycle in nontreated animals (Fig. 3). Although the characteristic "placental spotting of pregnancy" was noted in each of these control animals, it was not associated with the early, complete depression of progestin secretion seen with the treated animals. No significant undesirable drug related side effects were noted in any of the treated animals.

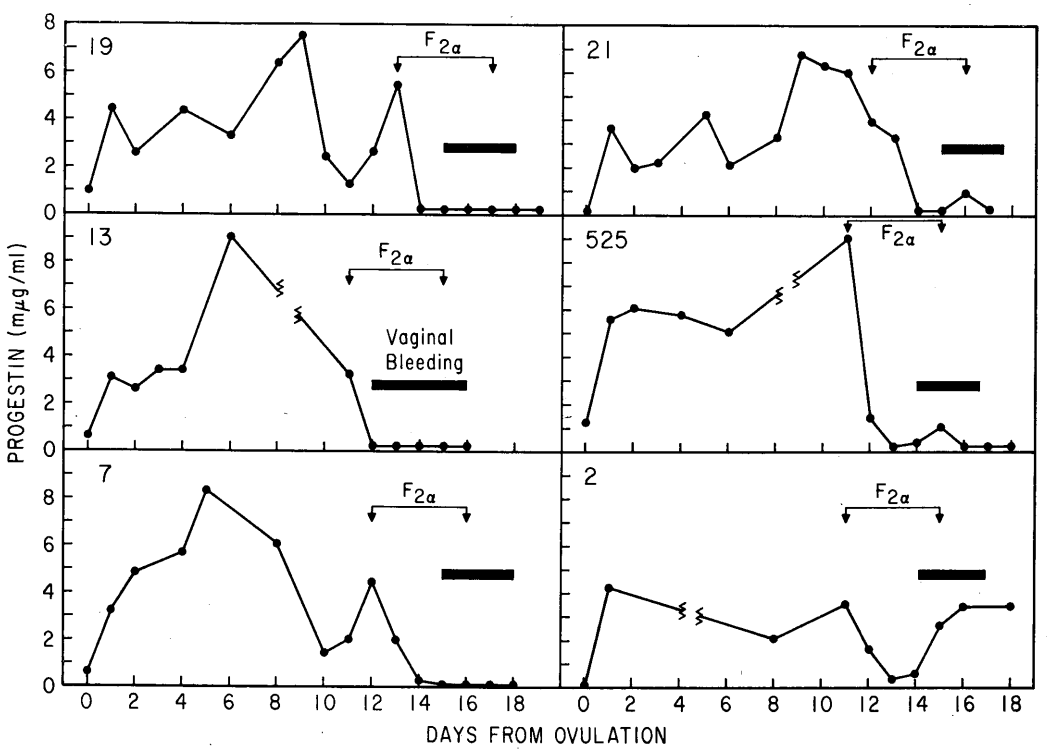

FIG. 2. Peripheral plasma progestin levels of mated rhesus monkeys injected with prostaglandin $F_{2\alpha}$.

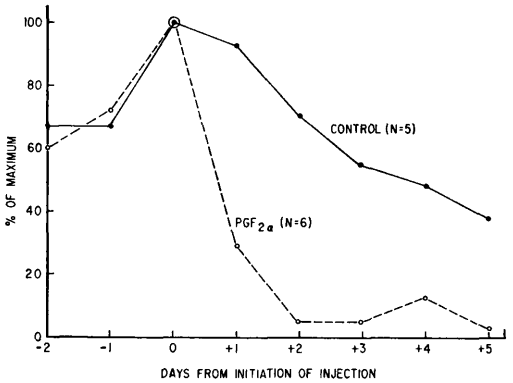

FIG. 3. Comparative decline in progestin level of treated and control animals.

Discussion. A lytic effect of the uterus on the corpus luteum has been demonstrated in most laboratory and many domestic animals studied to date. However, such a relationship has yet to be conclusively demonstrated in primates. The functional life of the human corpus luteum apparently is prolonged by hysterectomy during the early luteal stage of the menstrual cycle (7), in contrast, hysterectomized rhesus monkeys ovulate at regular intervals (8). Therefore, the role of the uterus in regulating corpus luteum function during the normal primate reproductive cycle has not been established. Data of the present experiment may indicate a luteolytic mechanism other than that which regulates the normal primate menstrual cycle. However, prostaglandin F_{2a} was luteolytic when injected early in the fertile cycle of rhesus monkeys. Treatment at this stage of the cycle definitely depressed progestin levels (Fig. 3). The rapidity with which these levels were depressed would suggest that treatment for 1 or 2 days may have been sufficient to initiate an unalterable chain of events which terminated in a complete demise of the corpus luteum.

The high levels of circulating progestin at the time of treatment initiation, days 11–13 postovulation, is due to stimulation from the blastocyst. Although this trophic effect may be secondary, mediated through the uterus or another organ, the corpus luteum is the primary, and indispensable, source of progesterone at this stage of pregnancy in the rhesus monkey (4). Therefore, the luteolytic effect of PG-F_{2a} is apparently mediated through, or at, the ovary.

Inability of PG-F_{2a} to completely suppress progestin levels, or to shorten the menstrual cycle when administered earlier in the luteal phase of the cycle, indicates that the corpus luteum of the monkey is more vulnerable to the luteolytic mechanism of this compound while stimulated by the blastocyst during the early stages of pregnancy.

Although the mode of action for the luteolytic activity of PG-F_{2a} is not definitely known, experimental evidence gained in other species implicates direct action on the corpus luteum, rather than mediation through the pituitary gland or the uterus (5). This evidence, and the data obtained in the present experiment indicate that prostaglandin F_{2a} should be useful in regulating primate reproductive cycles.

Summary. Prostaglandin F_{2a} was luteolytic in rhesus monkeys when injected 30 mg/day subcutaneously b.i.d. for 5 days, if the injections were initiated on day 11, 12, or 13 postovulation of fertile cycles. At this time circulating progestin levels are elevated, presumably due to a trophic stimulus from the blastocyst. Such an effect was not obtained by injection earlier in the luteal phase of the reproductive cycle. This indicates that the corpus luteum of this species is more vulnerable to luteolysis in the later stages of the reproductive cycle.

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