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Periparturitional Serum Concentrations of Prolactin, The Gonadotropins, and the Gonadal Hormones in the Rhesus Monkey[1] (39155)

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Parturition in the rhesus monkey is associated with marked alterations in circulating progesterone and estrogen concentrations (1–5). This study further describes the hormonal patterns characteristic of late gestation, parturition, and early lactation in this species.

Materials and methods. Blood samples were collected daily by femoral venipuncture from seven pregnant rhesus monkeys (*Macaca mulatta*) beginning 1 month prior to the estimated day of delivery and continuing until 1 month after parturition. All animals had normal, spontaneous deliveries between Days 156 and 172 of pregnancy (mean, 167 days) and nursed their young. The housing and husbandry of the monkeys has been previously described (6).

Serum LH and FSH concentrations were determined by specific radioimmunoassays (7, 8). Their minimal limits of sensitivity, using 200 μl of serum, were 2 ng/ml of our RhLH standard, WDP-X-47-BC (biopotency = 1.9 × NIH-LH-S1) and 10 ng/ml of our RhFSH standard, WDP-XI-93-4546 (biopotency = 14 × NIH-FSH-S1).

Prolactin was measured by a double antibody radioimmunoassay using a specific rabbit antiserum (#5P) to ovine prolactin and a rhesus monkey prolactin preparation as standard (9). The assay used here antedated the cited method and differed from it only in that a different rhesus prolactin preparation was used for the trace (WDP-XI-59-93) and ^{125}I was used for iodination. The direct assay of prolactin concentrations in unfractionated sera from normal adult or hypophysectomized monkeys showed inhibition curves that were not parallel to each other, nor parallel to the similar inhibition curves obtained with the standard prolactin preparation, a pituitary extract, or prolactin isolated from serum by Sephadex G-100 exclusion chromatography. Because the lack of parallelism between serum samples and standards could not always be systematically corrected by arithmetic manipulations based on the effect of serum from hypophysectomized monkeys, none of the prolactin values determined by this assay have been corrected for serum effects. Although this may have introduced an error, the trends observed in the time course of prolactin were unaffected, as shown in a subsequent study on five pregnant monkeys in which a more highly purified rhesus prolactin preparation was used as a trace, and ^{131}I was employed for iodination. These technical improvements markedly reduced the nonspecific serum effects and improved the precision and reproducibility of the assay (9).

Serum estrone and estradiol concentrations were determined by radioimmunoassay using Sephadex LH-20 chromatography to isolate the estrogens (10). The lower limits of detectability for both estrone and estradiol were 12.5 pg/ml. Serum progesterone levels were measured by a specific radioimmunoassay (11) with a sensitivity of 0.1 ng/ml.

The normal preparturient pattern of rising serum estradiol concentrations was replicated in two pregnant monkeys beginning on Days 92 and 95 of pregnancy by a regimen of daily subcutaneous injections of es-

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tradiol benzoate in oil (30 μg/kg for 4 days, 60 μg/kg for 3 days, and 120 μg/kg for 13 days).

Results. Estrogens. During the last 3 weeks of pregnancy, serum concentrations of estradiol (Fig. 1) were higher than the peak levels observed during the normal menstrual cycle (12). One week before parturition, circulating levels of estradiol and estrone began to increase, reaching a maximum of about 700 pg/ml and 350 pg/ml, respectively, on the day before delivery (Fig. 1). After parturition, estrone and estradiol levels fell precipitously to approximately 25 pg/ml. These concentrations, which are below those observed during the follicular phase of the menstrual cycle (12), were maintained throughout the 30-day postpartum observation period.

Progesterone. During the last week of gestation, serum progesterone levels also showed a sustained increase (Fig. 1). Progesterone concentrations fell abruptly after delivery to about 50% of prepartum levels, then slowly declined during the first month of lactation, but in confirmation of a previous report (13), remained at higher values than those observed during the follicular phase of the menstrual cycle.

LH and FSH. Serum concentrations of LH and FSH were either below or just at the lowest level of sensitivity of our assays throughout the period of observation (data not shown).

Prolactin. During the last week of pregnancy serum prolactin concentrations began to increase, reached maximum levels on the day of parturition, and then declined gradually during the early lactation period (Fig. 1). Using the improved radioimmunoassay for prolactin, a similar time course of increasing serum prolactin concentrations prior to delivery was observed in another group of five pregnant monkeys (Fig. 2), although the absolute serum prolactin concentrations were higher.

Estradiol administration to pregnant monkeys. As shown in Fig. 3, serum estradiol concentrations in Monkey #818 were increased, by the administration of estradiol benzoate, in a pattern similar to that seen in prepartum monkeys and plateaued at levels greater than those normally observed (Fig. 1). The other animal responded similarly. The pregnancies continued after the estrogen treatment and each monkey delivered a healthy infant at normal term.

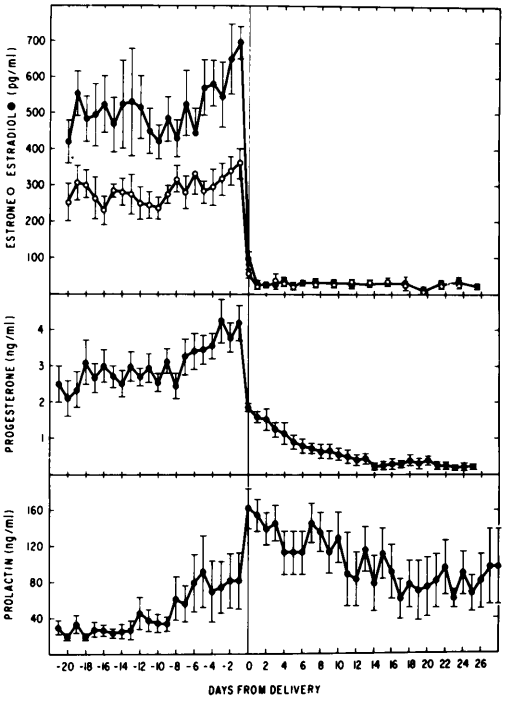

FIG. 1. Serum concentrations of estradiol, estrone, progesterone, and prolactin in seven rhesus monkeys before and after delivery on Day 0. Points are means ± standard errors.

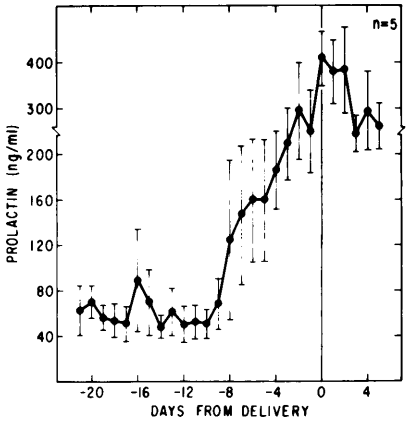

FIG. 2. Serum prolactin concentrations before and after delivery (Day 0) in five additional rhesus monkeys using a modification of the prolactin radioimmunoassay employed in Fig. 1. See text for details. Points are means ± standard errors.

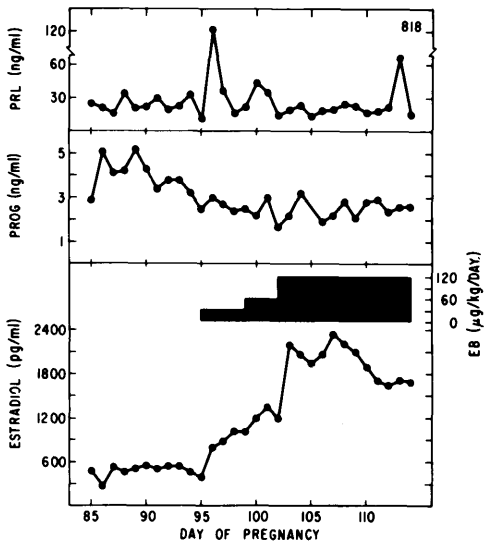

FIG. 3. Replication of the preparturitional estradiol pattern beginning on the 95th day of gestation by the administration of estradiol benzoate (EB) in increasing doses to a rhesus monkey. Pregnancy was not interrupted.

The estrogen treatment, while resulting in supraphysiologic circulating levels of estradiol, did not effect a significant, sustained increase in serum prolactin concentration.

Discussion. Parturition in the rhesus monkey is preceded by an abrupt, 5-fold elevation in serum prolactin concentrations during the last week of gestation. Estrogen and progesterone concentrations are also increased during this period in agreement with previous reports (1–5). While the parallel increase in estrogens and prolactin during the week preceding parturition may suggest a causal relationship (14), an acute stimulatory effect of estradiol on prolactin secretion has not been demonstrated in the rhesus monkey (9). Similarly, although it may have been tempting to speculate that the rising levels of progesterone are due to rejuvenation of the corpus luteum of pregnancy (15), perhaps in response to a luteotropic action of prolactin,these increases in serum progesterone concentrations occur after the corpus luteum has been removed (16).

Our observations that the replication of preparturitional circulating estrogen paterns in midgestation did not terminate pregnancy are in accord with those of Challis *et al.* (4), performed in late gestation. These findings do not support the hypothesis that the increase in circulating estrogens, per se, is the initiator of parturition in the rhesus monkey.

The serum estrogen concentrations during the first month of lactation, which are below those observed during the menstrual cycle (12), presumably reflect the profound reduction in gonadotropin levels also observed during this time. In women, this same phenomenon has been attributed to an inhibitory action of prolactin on gonadotropin secretion (17). Whether this apparent inverse functional relationship between prolactin and gonadotropin levels is also applicable to the rhesus monkey remains to be determined.

Summary. The time courses of serum concentrations of prolactin, estradiol, estrone, progesterone, LH, and FSH were studied in seven pregnant rhesus monkeys from 1 month prior to delivery until 1 month after parturition. All animals nursed their young. Circulating levels of estradiol and estrone increased during the last few days of pregnancy, reaching peak values of 700 pg/ml and 350 pg/ml, respectively, on the day prior to delivery, fell precipitously to about 25 pg/ml within 1 day after parturition, and remained at this level for at least 30 days. Serum prolactin concentrations also increased during the week preceding parturition, rose abruptly at delivery, and then declined gradually. Serum progesterone levels ranged between 2 and 3 ng/ml during the last month of pregnancy, rose slightly a few days prior to parturition, decreased sharply at delivery to 50% of prepartum levels and declined gradually thereafter. Serum LH and FSH levels were not detectable during the entire sampling period.

The administration of estradiol benzoate to two pregnant monkeys at midgestation, in a manner which replicated the normal prepartum increase in serum estradiol concentrations, failed to elicit an elevation in circulating prolactin levels or to induce premature delivery of the fetus.

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