

Fetectomy Alters Maternal Pituitary-Adrenal Function in Pregnant Rhesus Macaques¹

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ABSTRACT

The interplay between the fetus and mother may play a key role in the regulation of primate pregnancy and parturition. This study was designed to test the hypothesis that fetectomy alters maternal pituitary-adrenal function. Between 117 and 122 days of gestation (term = 167 days), six rhesus macaques underwent surgery for catheter implantation. At surgery the fetuses were removed while the membranes and placenta were left in situ. Six additional intact catheterized pregnant animals served as controls. Animals were maintained under a 12L:12D cycle with lights-on from 0700 to 1900 h. Beginning at least 1 wk after surgery, maternal arterial blood samples were collected at 3-h intervals for 24 h for hormone and catecholamine analysis. This sampling protocol was repeated at weekly intervals until cesarean delivery at 151–157 days of gestation. Following fetectomy, plasma ACTH, dehydroepiandrosterone sulfate (DHEAS), and cortisol levels were significantly lower (36%, 35%, and 44%, respectively) compared with control animals ($P < 0.05$). Despite a significant reduction in overall levels, the rhythm in maternal plasma cortisol was maintained following fetectomy. Plasma dopamine and norepinephrine were also depressed ($P < 0.05$), whereas epinephrine remained unaffected. Our data clearly demonstrate the role of the fetus in the regulation of the maternal pituitary-adrenal axis during gestation. This interaction plays a significant role in the regulation of maternal endocrine function that may influence the initiation of labor.

adrenocorticotropic hormone, catecholamines, cortisol, placenta, pregnancy

INTRODUCTION

The maternal endocrine changes that occur during the course of gestation are quite remarkable. Substantial increases in maternal plasma steroids, including estrogen and progesterone, as well as protein hormones, have been well documented in both human and nonhuman primate pregnancies [1–3]. The majority, if not all, of these changes appear to be induced by the presence of the fetus and its influence on the maternal endocrine system. The ongoing interactions between mother and fetus have been the focus of many studies attempting to understand the factors maintaining pregnancy and the final act of labor and delivery [2, 4–7].

Using the chronically catheterized rhesus monkey mod-

el, studies from our laboratory [5, 7–9] as well as those of others [10, 11] have clearly described the fetal and maternal endocrine changes during gestation. Data from these studies revealed the presence of 24-h rhythms in steroid and catecholamine concentrations. We suggest that these rhythms, particularly those of progesterone and estradiol, are intimately linked to rhythms in uterine activity. The role of the fetus in regulating maternal hormone concentrations has been examined by the use of fetectomized animals. In this experimental preparation, the fetus is removed during the later part of gestation, while the placenta and membranes remain in situ. Previous studies in baboons [4] and rhesus monkeys [7, 12] showed a significant decline in maternal plasma estradiol concentrations following fetectomy. The placenta, however, maintains much if not all of its functional endocrine capacity [13]. More recently, we demonstrated that fetectomy not only lowered maternal plasma and estradiol concentrations, but also eliminated the 24-h rhythm in rhesus monkeys [7]. Because estrogen has been suggested to alter hypothalamic-pituitary-adrenal axis function as well as catecholamine secretion [11, 14–16], we were interested in the effects of reduced estrogen levels following fetectomy on pituitary-adrenal function in the pregnant rhesus monkey.

In the present study, we examined longitudinal changes in maternal ACTH, dehydroepiandrosterone sulfate (DHEAS), cortisol, and catecholamine concentrations following fetectomy. Specifically, we tested the hypothesis that removal of the fetus would result in a suppression of maternal pituitary-adrenal function.

MATERIALS AND METHODS

Animals and Surgical Procedures

Pregnant rhesus monkeys of known gestational age were obtained from the California Regional Primate Center (Davis, CA). All procedures were performed as previously described in detail [7] and approved by the Loma Linda University Institutional Animal Care and Use Committee. The animals were acclimated to a controlled environment with a 12L:12D cycle (lights-on 0700–1900 h; light intensity 350 lux) and were fed ad libitum. A dim red light (<5 lux) remained on from 1900 to 0700 h to facilitate nocturnal blood sample collection.

Twelve animals were divided equally between control and fetectomy groups. Surgery was performed under halothane anesthesia between 117 and 122 days of gestation. At this time, catheters were implanted into a maternal femoral artery and vein, and in the amniotic fluid, and exteriorized as previously described [5, 7]. In the fetectomy group, the umbilical cord was also ligated and transected, and the fetus was exteriorized and removed, while the membranes and placenta were left in situ. Following surgery, all animals were maintained in a primate vest and tether catheter protection system to which they were previously acclimated [17]. All studies were initiated a minimum of 5 days after surgery.

Sampling Protocol

Maternal arterial blood samples were collected for determination of ACTH, cortisol, DHEAS, and catecholamine concentrations at 3-h inter-

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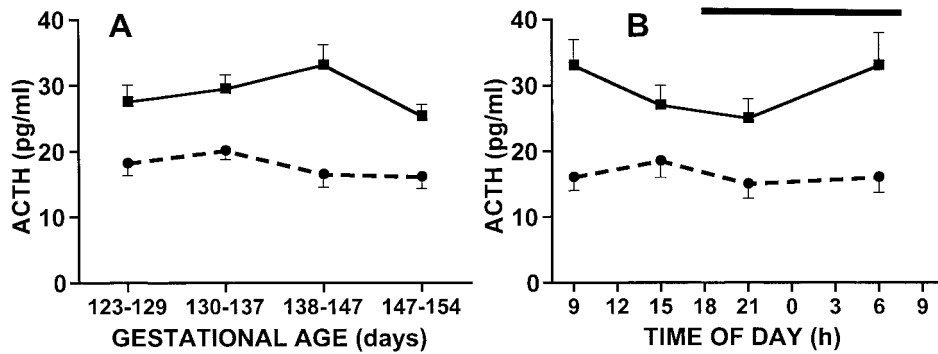


FIG. 1. Maternal plasma ACTH concentrations in control (■) and fetectomized (●) rhesus monkeys. **A**) Data represent samples collected at different gestational ages. Values for the fetectomy group were significantly lower compared with those for controls ($P < 0.05$). For this and all subsequent figures, values represent means \pm SEM of samples measured over a 24-h period for each group at each gestational age range. **B**) Plasma ACTH concentrations measured over 24-h sampling periods. Because the patterns were similar at each gestational age for each group, the data were combined to present one 24-h profile for the hormone of interest for each treatment group. This is also illustrated in subsequent figures. Values for each time point were significantly lower in the fetectomized group compared with those for controls ($P < 0.05$). The dark horizontal bar represents hours of darkness. All values represent means \pm SEM. Fetectomy was performed between Days 117 and 122 of gestation.

vals for 24 h starting at 0900 h. This sampling protocol was performed four times at weekly intervals for each of the following gestational age ranges: 123–129, 130–137, 138–146, and 147–154 days. Samples were collected in chilled tubes containing EDTA for ACTH, cortisol, and DHEAS, and tubes with EGTA for catecholamines. Blood was centrifuged at $3500 \times g$, and the plasma was separated and stored at -70°C until analyzed. Maternal erythrocytes were washed in sterile normal saline, resuspended, and returned to the maternal circulation.

Steroid Assays

Plasma concentrations of DHEAS and cortisol were determined by radioimmunoassay (RIA) at the Oregon Regional Primate Research Center Radioimmunoassay Core Laboratory as previously described, and validated RIA methods [5, 18]. The intraassay and interassay coefficients of variation for plasma DHEAS and cortisol RIAs were $<12\%$, whereas assay sensitivities were 0.2 and 0.7 pg/tube for DHEAS and cortisol, respectively.

ACTH Assay

Plasma concentrations of ACTH were analyzed by RIA using a commercial kit (IncStar Corp., Stillwater, MN) by methods that we have previously described and validated [5, 19]. The intraassay and interassay coefficients of variation for rhesus maternal plasma were less than 10%. Assay sensitivity (defined as the smallest amount of ACTH per RIA tube that reduces the number of counts per minute of labeled ACTH bound at zero mass by two standard deviations) was 0.5 pg/tube.

Catecholamine Analysis

Plasma concentrations of catecholamines were analyzed using high-performance liquid chromatography with electrochemical detection by methods previously described and validated in our laboratory [9, 20]. Briefly, catecholamines were separated from plasma and concentrated using alumina extraction. Dihydroxybenzylamine (DHBA) was added to the samples as an internal standard prior to extraction. Following desorption

from the alumina, norepinephrine, epinephrine, and dopamine were quantified using a Waters 700 Satellite WISP autoinjector, Waters 460 electrochemical detector, and a Waters 510 pump with a Resolve C18 column (Waters, Milford, MA). Recoveries for individual samples ranged from 70% to 85%, and the appropriate corrections were made. The intraassay coefficient of variation was less than 8% and the analysis system had a sensitivity range of 10–15 pg.

Data Analysis

To examine gestational age changes in hormone concentrations between treatment groups, the 24-h values for each group at each gestational age range were used. Data were analyzed by two-way ANOVA with repeated measures. Differences in maternal plasma hormone concentrations between treatment groups with time of day were also determined by two-way ANOVA with repeated measures. Because the patterns were similar at each gestational age for each group, the data were combined to present one 24-h profile for each hormone of interest.

RESULTS

Maternal plasma immunoreactive ACTH concentrations across the four gestational age sampling periods are illustrated in Figure 1A. Following fetectomy, ACTH concentrations were approximately 36% lower for the fetectomized animals compared with controls throughout the course of the study ($P < 0.05$). In an effort to determine potential effects of fetectomy on 24-h patterns of ACTH secretion, we also examined ACTH concentrations over 24-h collection periods at each of the gestational ages. The data in Figure 1B illustrate the mean values over the four gestational ages. Although there was a general trend for elevated ACTH levels in the morning, no significant pattern was noted. Like the controls, no pattern in ACTH secretion was associated with time of day in the fetectomy group. How-

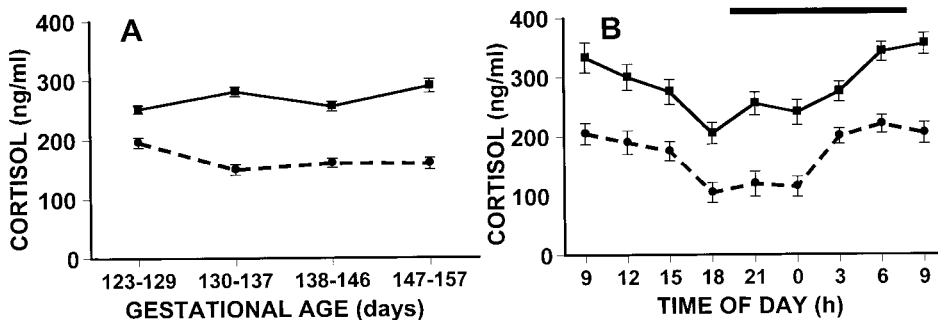
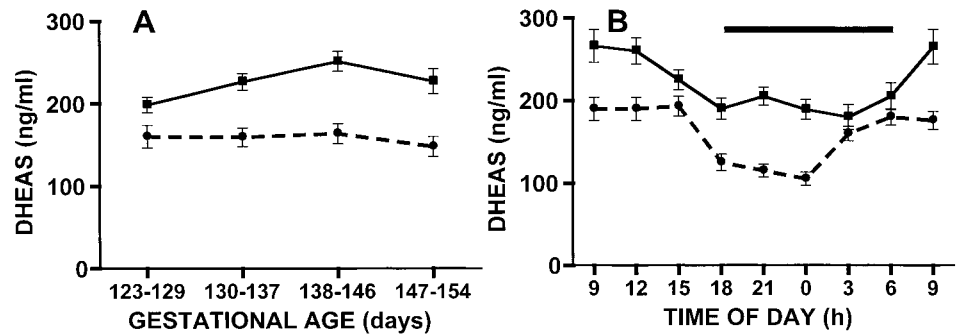


FIG. 2. Maternal plasma cortisol concentrations in control (■) and fetectomized (●) rhesus monkeys. **A**) Cortisol concentrations at different gestational age ranges. Values for the fetectomy group were lower than those for controls ($P < 0.05$). **B**) Plasma cortisol levels over 24-h sampling periods with the dark horizontal bar illustrating hours of darkness. Values for the fetectomy group were significantly lower compared with those for controls ($P < 0.05$). All values represent means \pm SEM.

FIG. 3. Plasma DHEAS concentrations in control (■) and fetectomized (●) rhesus monkeys. **A**) Data represent samples collected at different gestational ages. Values were lower in the fetectomized group compared with those for controls ($P < 0.05$). **B**) DHEAS concentrations during the 24-h sampling protocol. Values were lower in the fetectomized group compared with those for controls ($P < 0.05$). The dark horizontal bar depicts hours of darkness. All values represent means \pm SEM.



ever, ACTH levels were significantly lower at each time of day sampled (Fig. 1B).

To determine the effects of reduced ACTH concentrations following fetectomy, we examined changes in maternal cortisol concentrations. Like ACTH, maternal plasma cortisol concentrations were significantly reduced ($P < 0.05$) following fetectomy at each of the gestational ages examined (Fig. 2A). However, no significant changes were observed across gestation in either group. Twenty-four hour sampling (Fig. 2B) revealed a significant elevation in plasma cortisol in both groups between 0600 and 0900 h in both groups, with all values being higher in the control group compared with the fetectomized group ($P < 0.05$). In a similar manner, plasma DHEAS concentrations did not change remarkably across the gestational ages studied (Fig. 3A). However, fetectomy had a profound effect on mean levels, with a significant reduction noted at each gestational age when compared with controls ($P < 0.05$). Although the levels of DHEAS in the fetectomy group were lower than controls across the 24-h sampling periods, no diurnal pattern was observed in either group.

Plasma epinephrine concentrations were unaffected by fetectomy. No differences were observed across gestation (Fig. 4A), and both control and fetectomized animals exhibited the characteristic nocturnal nadir in epinephrine concentrations during the 24-h sampling protocols (Fig. 4B). In marked contrast, both norepinephrine (Fig. 5A) and dopamine (Fig. 6A) were significantly lower across gestation in the fetectomized animals compared with control ($P < 0.05$). The most striking change occurred with dopamine, with concentrations falling almost 10-fold following fetectomy. No 24-h patterns were observed for either norepinephrine (Fig. 5B) or dopamine (Fig. 6B) in either control or fetectomized animals.

DISCUSSION

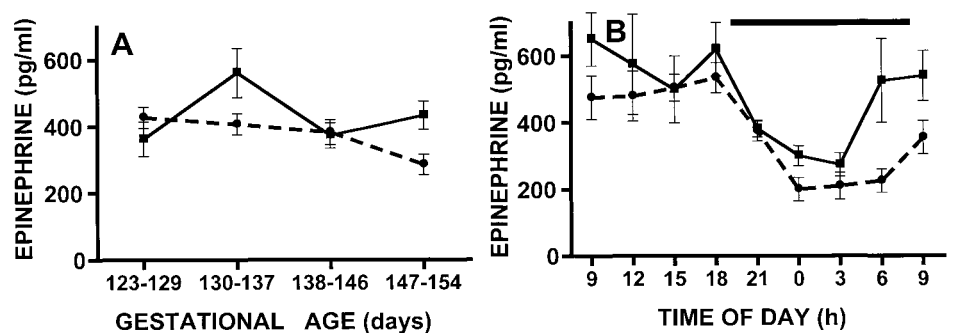
Results of the present study clearly demonstrate an inhibitory effect of fetectomy on the maternal pituitary-ad-

renal axis in the late-gestation rhesus monkey. Specifically, maternal plasma ACTH, cortisol, and DHEAS concentrations were significantly lower in fetectomized animals compared with intact controls. This occurred within 1 wk of removal of the fetus and was maintained over the entire course of the study. In addition, catecholamine secretion (norepinephrine and dopamine) was also reduced in the fetectomized animals. To our knowledge, this study is the first to demonstrate the effects of fetectomy on maternal pituitary-adrenal function in the pregnant, nonhuman primate.

Maternal/fetal endocrine communication appears to play a key role in the initiation of labor. In the sheep, the classic studies by Liggins and coworkers [21] clearly demonstrated the role of the fetus in the regulation of parturition. Removal of the fetus (fetectomy) or fetal death disrupted the normal timing of delivery [22]. However, in the nonhuman primate, the role of the fetus in the regulation of gestational length remains somewhat controversial. Early fetectomy studies in rhesus monkeys showed that delivery of the placenta occurred within a wide range of gestational ages, with the authors concluding that labor was independent of the fetus [23]. Additional information in the baboon is consistent with this concept [24]. More recent studies by Nathanielsz et al. [6], however, suggest that the fetus plays a major role in determining the length of gestation in the rhesus monkey. Such information further highlights the enigmatic nature of the fetus in the regulation of gestational length in the nonhuman primate.

The endocrine effects of fetectomy in the primate have been only partially elucidated. We have previously demonstrated that fetectomy resulted in the decline of maternal estradiol and progesterone concentrations and a loss of the estradiol rhythm [7]. These data are in agreement with earlier studies in the baboon [4]. We further determined that fetectomy resulted in a loss of the uterine activity [7]. We hypothesized that the fetus, by supplying estrogen precursors, may play an indirect role in the generation of maternal estradiol rhythms.

FIG. 4. Maternal plasma epinephrine concentrations in control (■) and fetectomized (●) rhesus monkeys. **A**) Plasma epinephrine concentrations at different gestational ages. **B**) Epinephrine concentrations across the 24-h sampling protocol with hours of darkness represented by the horizontal bar. All values represent means \pm SEM.



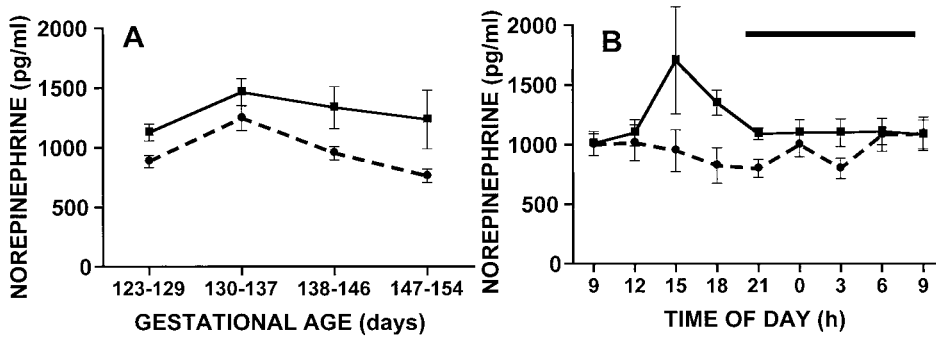


FIG. 5. Maternal plasma norepinephrine concentrations in control (■) and fetectomized (●) rhesus monkeys. A) Plasma norepinephrine at different gestational ages. Mean values were significantly lower in the fetectomized animals compared with those in controls ($P < 0.05$). B) Norepinephrine concentrations during the 24-h sampling protocol. All values represent means \pm SEM and the hours of darkness are represented by the horizontal bar.

In the present study, the reduction of maternal estradiol concentrations following removal of the fetus may also play a role in the reduction of maternal ACTH secretion. A number of studies have demonstrated a stimulatory effect of estrogen on the hypothalamic-pituitary-adrenal (HPA) axis. In the rat, estradiol treatment results in enhanced ACTH and cortisol responses to stress [25] as well as elevated pituitary ACTH content [26]. Estrogen also appears to have a stimulatory effect on ACTH in the nonhuman primate. Estradiol 17- β administration to postpartum baboons resulted in a significant rise in plasma ACTH concentrations with a concomitant increase in circulating cortisol and DHEAS [14]. In the baboon fetus, pituitary expression of proopiomelanocortin has also been shown to increase following maternal estrogen treatment at midgestation [27]. This increase was believed to result from changes in placental metabolism/transport of bioactive cortisol into the fetus. Data from nonpregnant rhesus monkeys also reinforce the role of estrogen in the regulation of the maternal HPA axis. Nighttime ACTH concentrations measured in seasonally anovulatory animals with very low plasma estradiol concentrations [28] were similar to the reduced values observed in our fetectomized animals. In addition, Koritnick et al. [29] found that plasma DHEAS concentrations in nonpregnant animals were about 35% lower than in pregnant animals. This percentage is similar to the difference between our intact and fetectomized animals. Taken together, these data strongly support a role for estrogen in the regulation of ACTH secretion. In the present study, the observed attenuation of maternal plasma ACTH concentrations is consistent with the reduced estrogen levels in these fetectomized animals (reported in [7]).

An alternative hypothesis centers on the potential role of placentally derived corticotropin-releasing factor (CRF) and ACTH. These peptide hormones are secreted in forms that are structurally and functionally indistinguishable from their neurally derived counterparts [30, 31]. Placental CRF stimulates output of proopiomelanocortin-derived peptides

from the placenta including ACTH, which are unaffected by glucocorticoid levels [31, 32]. In addition, immunohistochemical methods localized CRF to syncytiotrophoblast and intermediate trophoblast tissue in the placenta [33]. Although the relative contribution of placental CRF to maternal plasma levels is unknown, comparison of CRF concentrations in nonpregnant vs. pregnant women suggests a significant contribution by the placenta [34]. This suggestion is further strengthened by the observation that ACTH is also elevated during pregnancy compared to the nonpregnant state [34].

The direct effects of fetectomy on production of placental CRF, ACTH, or both are unknown. However, if placental growth is impaired following fetectomy, placental production of these peptides may also be compromised. From a structural standpoint, the fetal surface of the placenta becomes devascularized while the syncytiotrophoblast remains the predominant placental villous cell type [35]. Actual growth of the placenta following fetectomy is equivocal. Placental weights from animals in the present study were presented elsewhere [7]. Because we were unable to measure the placental weight at the time of fetectomy, the placental weights at the time of cesarean delivery were used to estimate the weight at fetectomy. Two different formulas were used based on studies by Cheek [36] and van Wageningen and Catchpole [37]. One estimate suggested that the placenta continued to grow after fetectomy while the other indicated a cessation of growth. The latter result is in agreement with earlier data in the baboon [35] and rhesus monkey [6] suggesting a lack of growth after fetectomy. Although fetectomy may impair placental growth it appears that it does not alter at least one aspect of placental endocrine function because the capacity for aromatization is maintained [13].

Whether changes in placental growth explain the significant reduction in ACTH observed in the present study is unclear. Although we did not measure CRF in the present study, data from Smith and coworkers [38] showed that

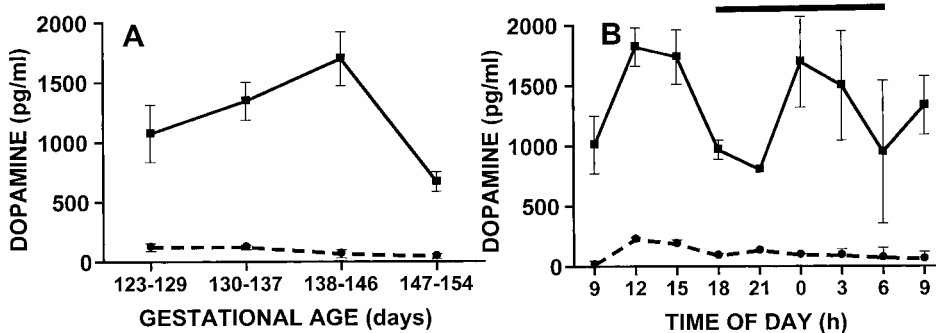


FIG. 6. Maternal plasma dopamine concentrations in control (■) and fetectomized (●) rhesus monkeys. A) Plasma dopamine concentrations at different gestational ages. Levels were significantly lower in the fetectomized group across the gestational intervals studied ($P < 0.05$, compared with controls). B) Twenty-four hour plasma dopamine concentrations. Values were lower in the fetectomized group compared with those for controls ($P < 0.05$). The horizontal bar illustrates hours of darkness. All values represent means \pm SEM.

CRF had a direct stimulatory effect on adrenal DHEAS production. Because DHEAS levels were significantly reduced, it is unlikely that CRF levels were maintained following fetectomy. Whether the decline in estradiol or a loss of placental CRF/ACTH is responsible for the dramatic reduction in ACTH following fetectomy, the end result is a significant reduction in maternal plasma cortisol and DHEAS.

The drop in DHEAS level in the fetectomized rhesus monkey is in marked contrast to data from the baboon. Albrecht and Pepe [39] found that maternal peripheral DHEAS concentrations did not change following fetectomy. Further, estradiol treatment in both intact and fetectomized animals resulted in a decline in DHEAS concentrations. The authors suggested that there is a negative feedback system in utero in the baboon, where placental estrogen regulates maternal and fetal adrenal androgen production. Based on data from the present study, it does not appear that a similar system exists in the rhesus monkey. Although this difference cannot simply be ascribed to species differences, there is a significant difference in plasma estradiol concentrations between the two. In the near-term baboon, peripheral estradiol concentrations reach approximately 2.5 ng/ml [40], whereas in the rhesus monkey, levels are less than 600 pg/ml [7]. This fourfold difference may account for the difference in feedback mechanisms.

Fetectomy may also affect cortisol metabolism. Under normal circumstances, corticosteroid-binding globulin is elevated under the influence of estrogen [41, 42]. Because estrogen levels are significantly reduced in fetectomized animals, corticosteroid-binding globulin concentrations may be suppressed, thereby enhancing cortisol metabolism. This may add to the effect of reduced ACTH levels on plasma cortisol concentrations.

Under normal conditions, approximately 50% of circulating catecholamines are from the adrenal medulla, while the rest is from ganglia or the autonomic nervous system. However, the origin of increased circulating catecholamines during pregnancy is unclear. Estrogen treatment decreased dopamine content in corpus striatum [43] and increased basal dopamine release [44]. Estrogen also produced a marked increase in the norepinephrine content in uterus, but not in heart and ovarian tissues [45]. These results suggest that estrogen may increase maternal circulating catecholamines during pregnancy. In the present study, fetectomy with the resultant decline in estrogen levels [7] resulted in a significant decrease in both dopamine and norepinephrine following fetectomy.

The most surprising finding is the enormous 10-fold drop in maternal plasma dopamine following fetectomy. We can only hypothesize the possible mechanisms of such a dramatic change. Studies in rhesus monkeys have shown a clear correlation between plasma estradiol concentrations and plasma dopamine-beta hydroxylase activity [46]. High estrogen levels during the cycle resulted in depressed levels of this enzyme. Further, ovariectomized animals exhibited significantly higher activity than intact controls. Platelet monoamine oxidase activity was also higher in ovariectomized animals. Studies in women have also demonstrated an inhibitory effect of estrogen plasma dopamine-beta hydroxylase activity [47]. We speculate that perhaps in the present study, the reduction in estrogen concentrations following fetectomy could result in an increase in dopamine-beta hydroxylase activity, thus resulting in a reduction in plasma dopamine concentrations. Unfortunately, to our knowledge, there are no data regarding alterations in do-

pamine-beta hydroxylase activity during pregnancy in the nonhuman primate.

The lack of effect of fetectomy on epinephrine concentrations is also puzzling because ACTH stimulates tyrosine hydroxylase [48, 49]. Further, glucocorticoids such as cortisol increase the synthesis and secretion of epinephrine from the adrenal medulla through stimulation of phenylethanolamine *N*-methyltransferase [50]. In the present study, the reduction in ACTH and cortisol after removal of the fetus would be expected to result in reduced epinephrine concentrations. However, both basal levels and the diurnal rhythm were maintained. There is precedence for this apparent dissociation of adrenal medullary and cortical secretion. We have previously shown that under constant lighting conditions, the diurnal rhythm in cortisol was retained, while the rhythm in epinephrine was ablated [5, 9]. The mechanism for this dissociation however, remains undefined.

In summary, fetectomy results in a suppression of maternal pituitary-adrenal function in the rhesus monkey during the latter part of gestation. The observed reduction in ACTH following fetectomy is coupled to decreases in both cortisol and DHEAS. Surprisingly, epinephrine secretion was unaffected, while plasma norepinephrine and dopamine concentrations were lower than intact animals of similar gestational age. These data, coupled with the reduced maternal estradiol concentrations and myometrial contractility [7] further strengthen the role of the primate fetus in the regulation of the maternal endocrine system. This maternal-fetal communication appears to play a key role in the endocrine events leading to the initiation of parturition.

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