Daily and hourly temporal association between Δ^4-androstenedione–induced preterm myometrial contractions and maternal plasma estradiol and oxytocin concentrations in the 0.8 gestation rhesus monkey

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OBJECTIVE: Our purpose was to investigate the temporal relationship between Δ^4-androstenedione-induced preterm switching of myometrial activity patterns from contractures to contractions and maternal plasma estradiol and oxytocin concentrations in the 0.8 gestation rhesus monkey.

STUDY DESIGN: Eight rhesus monkeys (132 to 136 days' gestation) were instrumented under halothane with femoral artery and vein catheters and uterine electromyogram electrodes. At 138 to 142 days' gestation baseline maternal femoral artery blood samples for estradiol and oxytocin measurement were taken at 30-minute intervals for 7 hours, starting 2 hours before the onset of darkness. The day after baseline sampling a continuous intravenous Δ^4-androstenedione infusion (0.3 mg · kg^{-1} · hr^{-1} in 10% intralipid at 0.25 ml · hr^{-1}) was started in four monkeys, while four monkeys were infused intravenously with intralipid alone. The sampling regimen was then repeated at 1 and 3 days after the start of the Δ^4-androstenedione or intralipid infusion. Contractions were counted and estradiol and oxytocin were measured by radioimmunoassay.

RESULTS: Androstenedione promoted a premature nocturnal increase in myometrial contractions in conjunction with an increase in maternal plasma concentrations of estradiol and oxytocin, which were of similar magnitude to those measured in spontaneous term labor. The increase in maternal estradiol preceded the increase in maternal oxytocin levels and myometrial contractions. The onset of the increase in maternal plasma oxytocin was closely associated with the appearance of myometrial contractions after Δ^4-androstenedione treatment. In contrast, no sustained premature contractions or changes in estradiol and oxytocin occurred in intralipid-treated monkeys.

CONCLUSIONS: We conclude that in the 0.8 gestation rhesus monkey (1) the increase in maternal plasma estradiol precedes the increase in maternal plasma oxytocin after Δ^4-androstenedione treatment and (2) Δ^4-androstenedione-induced preterm myometrial contractions are closely associated in time with physiologic increases in maternal plasma oxytocin concentrations. (Am J Obstet Gynecol 1996;174:1050-5.)

Key words: Labor, preterm labor, rhesus monkey, oxytocin, estrogen

The development of continuous measurements of uterine electromyographic activity with concomitant changes in intraamniotic pressure in nonhuman primate species by several groups of investigators has allowed the description of two types myometrial activity patterns: low amplitude, long-lasting contractures and prominent, short-lasting contractions.[1] In most species studied to date, including the human,[2] the baboon,[3, 4] and the rhesus monkey,[5-7] although myometrial contractures occur throughout the majority of pregnancy, the switch to myometrial contractions is an inherent prerequisite for spontaneous labor and delivery.

In the preparturient primate, including women, the switch from contractures to contractions has three special characteristics. First, the switch occurs around the onset of darkness.[3, 5, 8] Second, it is reversible. The night when spontaneous delivery occurs is generally preceded by a variable number of nights during which the switch from contractures to contractions reverts to contractures after

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a few hours of contraction activity.[5, 9] Finally, the switch is progressive, the number of nighttime contractions augmenting on consecutive nights until spontaneous delivery finally occurs.[9]

The mechanisms mediating the switch from contractures to contractions during spontaneous labor have been the focus of a number of investigations. In the primate a central role for mediating the switch from contractures to contractions has been attributed to estrogen-induced increases in maternal plasma oxytocin levels. Accordingly, the onset of spontaneous nighttime contractions is closely associated in time with elevated maternal plasma oxytocin concentrations,[5, 10] and use of oxytocin antagonists will abolish myometrial contractions in the monkey[5, 11] and in the baboon.[4] Although precise recording of myometrial activity is not possible in human pregnancy, oxytocin antagonists do appear to decrease myometrial activity in pregnant women.[12]

We have recently developed a model for inducing premature labor in the rhesus monkey at 0.8 gestation that reproduces the characteristics of the primate switch from myometrial contractures to contractions. Thus administration of Δ^4-androstenedione to the pregnant monkey at 0.8 gestation will induce premature nighttime, reversible and progressive epochs of myometrial contractions, an increase in maternal plasma estradiol and oxytocin concentrations, and live delivery.[6, 13] However, the temporal relationship between the increases in estradiol and oxytocin in maternal plasma and between increased maternal oxytocin and Δ^4-androstenedione–induced premature myometrial contractions has not been investigated to date. In the current study we investigated the effect of Δ^4-androstenedione treatment on the following events in the 0.8 gestation rhesus monkey: (1) the daily temporal relationship between maternal plasma estradiol and oxytocin and (2) the hourly temporal relationship between the onset of the increase in maternal plasma oxytocin levels and premature myometrial contractions.

Material and methods

Care of animals. Eight pregnant rhesus monkeys of known gestational age were obtained from the California Regional Primate Research Center (Davis, Calif.) and acclimated to laboratory conditions and to the tether restraint system, as previously described.[5, 9, 13, 14] In brief, after a full physical examination the animals were housed in individual cages in rooms with controlled light/dark cycles (14 hours light and 10 hours dark) and placed in quarantine. During quarantine the animals were jacketed and familiarized with the tether through which vascular catheters and electrode leads were to be connected after surgical instrumentation. One week later the tether was fixed to a box on the back of the jacket. The animals were fed daily (Purina 5045 High Protein Monkey Chow, Purina, St. Louis; and fresh fruits), and water was continuously available.

Surgical instrumentation and postsurgical management. The monkeys were instrumented between 118 and 136 days' gestation (term is approximately 163 days, see Table I) by techniques previously described.[5, 9, 13, 14] Following food deprivation for 24 hours, polyvinyl catheters (inner diameter 0.04 inch, outer diameter 0.07 inch; Tygon, Baxter, N.J.) were placed in the dorsal aorta and inferior vena cava through the left femoral artery and vein, respectively, while animals were under general anesthesia (15 mg · kg^{-1} ketamine for induction, 1% to 2% halothane in oxygen for maintenance). In addition, three pairs of multistranded electrodes (AS 632, Cooner Wire, Chatsworth, Calif.) were sewn on different sites of the anterior surface of the uterine body to monitor myometrial electromyographic activity. Catheters were filled with heparinized saline solution (25 IU ml^{-1}) and tunneled subcutaneously with the electrode leads to exit between the shoulder blades. After surgery the monkey was rejacketed and maintained on the tether-and-swivel system, which allowed the animal to be free ranging and permitted passage of vascular catheters and electromyographic leads to the top of the cage.[5, 9, 13, 14] The tether was attached to the box within the animal's jacket. At least 5 days was allowed to elapse before commencement of all experiments, during which time antibiotics (oxacillin, intravenous infusion of 100 mg · kg^{-1} · day^{-1}) and analgesics (buprenorphine, intraarterial infusion of 15 μg · kg^{-1} · day^{-1} for 2 days) were administered to the mother.

Treatment groups and blood sampling. Catheters were maintained patent by continuous infusion of heparinized saline solution (25 IU ml^{-1} at 0.5 ml · hr^{-1}) from surgery until the commencement of one of two treatments at 138 to 145 days' gestation (Table I). In four monkeys (control group) the saline solution administration was switched to a continuous infusion of intralipid vehicle alone (intralipid 10%, Kabi Vitrum, Alameda, Calif.) set at the same rate and in the other four monkeys (experimental group) Δ^4-androstenedione (4-androstenedione-3,17-dione, Sigma, St. Louis) dissolved in intralipid was infused continuously at 0.3 mg · kg^{-1} · hr^{-1}.

In all animals 15 blood samples were taken at 30-minute intervals for 7 hours during a baseline period starting 2 hours before the onset of darkness. In addition, 0.3 ml of arterial blood was taken at the beginning and end of the sampling period for measurement of pH, Pco_2, and Po_2. These sampling procedures were then repeated 1 and 3 days after the start of intralipid or Δ^4-androstenedione treatment.

All arterial blood samples for hormone analyses (4 ml) were collected under aseptic techniques and transferred into chilled polypropylene collection tubes. These were centrifuged at 4° C at 1200*g* for 5 minutes. Plasma was removed, aliquoted, flash-frozen, and stored at −20° C

Table I. Animals used during experimental protocol

Group	*Weight (kg)*	*Surgery (days' gestation)*	*Start of infusion (days' gestation)*	*Δ^4-Androstenedione ($mg \cdot kg^{-1} \cdot hr^{-1}$)*
Control				
Rh1	5.9	118	145	0.0
Rh2	7.3	132	138	0.0
Rh3	5.9	132	138	0.0
Rh4	6.8	136	142	0.0
Mean ± SEM	6.5 ± 0.3	129 ± 4	141 ± 2	0.0 ± 0
Experimental				
Rh5	5.9	121	139	0.30
Rh6	6.8	118	139	0.30
Rh7	10.9	136	142	0.30
Rh8	5.6	132	140	0.30
Mean ± SEM	7.3 ± 1.2	127 ± 4	140 ± 1	0.30 ± 0

Four monkeys (control group) were treated with intralipid and four (experimental group) with Δ^4-androstenedione.

Table II. Arterial blood gas and pH values in monkeys during baseline and 1 and 3 days after start of intralipid (control, $n = 4$) or Δ^4-androstenedione (experimental, $n = 4$) treatment

Group	*pH*	*$Paco_2$ (mm Hg)*	*Pao_2 (mm Hg)*
Control			
BL	7.424 ± 0.02	34.7 ± 0.8	111.5 ± 2.5
Day 1	7.452 ± 0.01	32.7 ± 0.1	113.1 ± 3.3
Day 3	7.428 ± 0.01	34.6 ± 0.8	110.2 ± 1.2
Experimental			
BL	7.442 ± 0.02	35.7 ± 1.4	99.7 ± 3.4
Day 1	7.459 ± 0.01	35.9 ± 1.4	107.4 ± 3.1
Day 3	7.439 ± 0	34.4 ± 2.3	108.1 ± 7.2

Values shown are mean ± SEM. *BL*, Baseline.

until assayed. Remaining red blood cells from the centrifuged tubes were resuspended in heparinized saline solution (25 IU ml^{-1}) and returned to the animal's arterial circulation.

Hormone analyses. Measurement of estradiol and oxytocin concentrations in rhesus monkey plasma was determined by radioimmunoassay. These assays have been validated for use in rhesus monkeys and the assay procedures previously described in detail. Maternal plasma estradiol was measured on duplicate 200 µl plasma aliquots.[14] Oxytocin was extracted with acetone from 1 ml plasma and duplicate 200 µl aliquots were measured.[5] The lower limit of detection of the assays, defined as 90% B/Bo, was 12 $pg \cdot ml^{-1}$ for estrogen and 1 $pg \cdot ml^{-1}$ for oxytocin. Intraassay and interassay coefficients of variation were 8.5% and 7.0% for estradiol and 8.8% and 12.7% for oxytocin, respectively.

Analyses of myometrial activity. Uterine activity was recorded continuously throughout the study period. Recording of the myometrial electromyographic activity was performed with a computer-based data acquisition system. The signal was sampled at 32 Hz and integrated, and the average over 8 seconds was digitized and stored with a time signal.[1] A switch in myometrial electromyographic activity to contractions was defined if at least six contractions, each lasting about 1 minute, occurred sequentially and the bout of contraction activity lasted ≥30 minutes. Individual contractions were counted visually.

Statistical analyses. Blood gases and pH are expressed as the mean ± SEM of each of the experimental periods: baseline, day 1, and day 3. For daily associations of plasma concentrations of estradiol and oxytocin to myometrial contraction activity, the mean of all 15 hormone samples and the total number of contractions within the 7-hour experimental period were calculated. For close association of plasma oxytocin to myometrial contraction activity, each sample taken at 30-minute intervals was plotted along with the number of contractions per 30-minute period for each animal.

Data for statistical analyses that were not normally distributed were log-transformed for endocrine parameters and square root transformed for contraction counts. Repeated-measures analysis of variance with Dunnetts multiple comparison tests was used to compare all measured variables between baseline and 1 or 3 days for both the control and experimental groups of animals. Significance was accepted when $p < 0.05$.

Results

Arterial blood gases and pH. Mean arterial blood gases and pH values were similar between intralipid- and Δ^4-androstenedione–treated monkeys during the baseline period. Furthermore, there were no differences in any of these variables measured after intralipid or Δ^4-androstenedione treatment (Table II).

Daily association of endocrine parameters to myometrial contractions. In control monkeys mean plasma estradiol and oxytocin levels and mean number of contractions remained unchanged from baseline 1 and 3 days after the start of the intralipid infusion (Fig. 1).

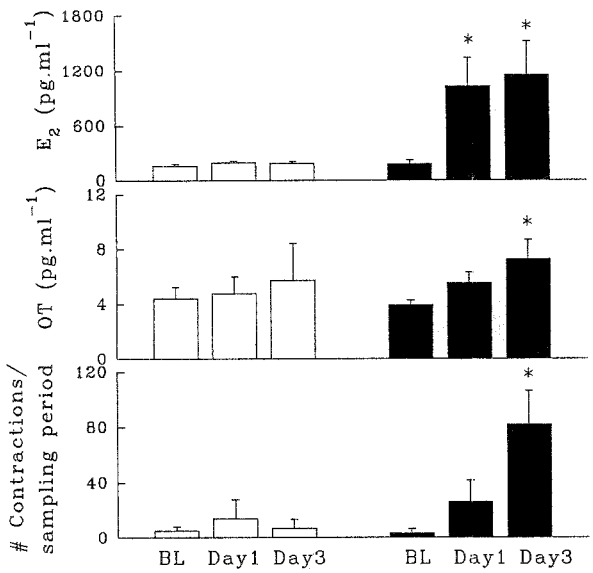

Fig. 1. Daily temporal relationship between maternal plasma concentration of estradiol *(E_2)* and oxytocin *(OT)* and number of contractions per sampling period during baseline *(BL)* and 1 to 3 days after intralipid (control, $n = 4$, *white bars*) or androstenedione (experimental, $n = 4$, *black bars*) treatment. *Asterisk*, $p < 0.05$.

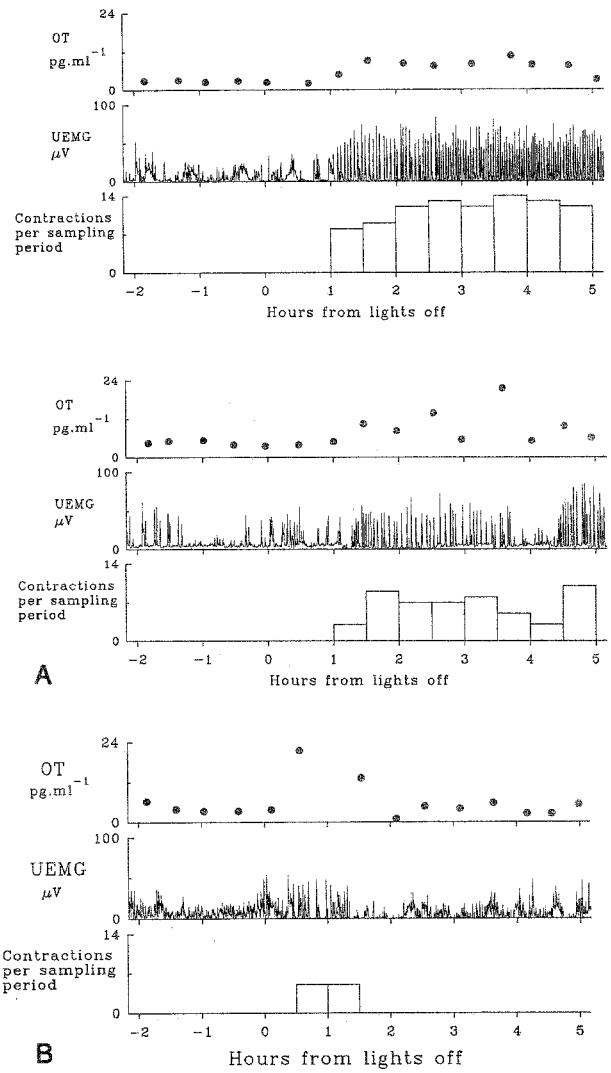

Fig. 2. Close relationship between maternal plasma oxytocin *(OT)* and uterine activity in two androstenedione-treated monkeys **(A)** and one monkey treated with intralipid **(B).** Blood samples for oxytocin measurement were taken every 30 minutes. Uterine activity is shown as raw data collected every 8 seconds and as number of contractions counted per 30-minute periods. *UEMG,* Uterine electromyographic activity.

In contrast, mean plasma estradiol increased after 1 day and remained elevated after 3 days of Δ^4-androstenedione treatment (Fig. 1). The increase in plasma oxytocin concentration by the third day after Δ^4-androstenedione was concurrent with an increase in the number of myometrial contractions.

Hourly association of plasma oxytocin concentrations to myometrial contractions. The relationship between changes in plasma oxytocin concentrations with the switch in myometrial activity to contractions in either day 1 or day 3 after Δ^4-androstenedione treatment is shown for two individual animals in Fig. 2, *A*. In addition, some control animals did occasionally undergo short periods of contraction activity that were not sustained during baseline and after intralipid treatment. An example of one intralipid-infused animal showing the relationship between these bouts of contractions and plasma oxytocin concentrations is shown in Fig. 2, *B*.

In all four Δ^4-androstenedione–treated monkeys and in control monkeys, which occasionally exhibited bouts of contractions, there was a close temporal association between the switch in myometrial activity to contractions and the increase in plasma oxytocin concentrations.

Comment

Because premature birth occurs in 7% of pregnancies and is responsible for 50% of long-term neurologic deficits and 75% of neonatal mortality,[15] a physiologic model for providing insight into complications during pregnancy that would lead to prematurity is of paramount importance. Although such a model has been established in sheep in which infusion of cortisol or corticotropin to the fetus at about 120 days' gestation (term 147 days) consistently induces premature delivery,[16] no such model exists to study premature birth in the primate.

Such a successful model in the primate must induce preterm labor by similar mechanisms mediating primate spontaneous term labor. Current evidence suggests that increased placental estrogen synthesis during gestation promotes parturition in both sheep[16] and primates,[17] although the source of this estrogen increase has been demonstrated to be very different between the two spe-

cies. This difference has been attributed to the lack of P_{450} 17α enzyme expression in the primate placenta.[18] In sheep this enzyme promotes estrogen synthesis from progesterone.[17] Increased fetal plasma cortisol induces P_{450} 17α placental expression. In primates increased placental estrogen production cannot be induced either from progesterone[18] or by maternally administered cortisol.[19] However, the primate placenta does express the enzyme P_{450} aromatase, which can promote estrogen synthesis from aromatizable placental precursors such as Δ^4-androstenedione.[18]

We have hypothesized that in the primate increased fetal adrenal androgen production leads to increased placental estrogens, their synthesis contributing to increased maternal plasma oxytocin concentrations and myometrial contractions. Accordingly, estrogens have been demonstrated to stimulate a number of maternal systems that are fundamental to activation of spontaneous myometrial contraction activity in the primate. For example, estrogens will increase oxytocin synthesis by the hypothalamus[20] and by intrauterine tissues[21] and lead to an increase in myometrial gap junctions.[22]

In spite of well-known descriptions of the uterotonic action of oxytocin, early doubts about its role in human parturition arose largely because some investigators reported an increase in human maternal plasma and amniotic fluid oxytocin at term and during labor but others failed to demonstrate these increases. This failure to demonstrate prepartum changes in oxytocin may reflect procedural problems rather than the lack of a rise in oxytocin. Two potential sources of negative results may have been the lack of specific assays with adequate sensitivity and sampling regimens that did not allow for the 24-hour rhythm that exists in maternal plasma oxytocin in the pregnant primate.[23] More recent reports using systematic and frequent blood sampling regimens for oxytocin measurement have now demonstrated the development of such a 24-hour pattern in oxytocin concentrations in both late-gestation monkeys[5, 9, 23] and women,[24] with the highest concentrations occurring in the early hours of darkness. In addition, the peak plasma nocturnal oxytocin levels are associated to the nocturnal transition to contraction-type myometrial activity in the pregnant monkey,[5] and the magnitude of oxytocin secretory peaks is increased with advancing gestation.[10] These studies thus provide a possible explanation for the apparent lack of increase in maternal plasma and amniotic fluid oxytocin concentrations reported by investigators who only took samples in the morning. In addition, abolition of spontaneous myometrial contractions by oxytocin antagonists in the pregnant monkey,[5, 11] baboon,[4] and woman[12] produced renewed support for a role for oxytocin in regulating myometrial contractions and labor in the primate. Additional data reporting an increase in oxytocin receptors in the human uterus during pregnancy and parturition[25] and an increase in oxytocin peptide and message in the amnion, chorion, and decidua in the rat[26] and human[21] confirm an association between oxytocin and parturition.

We have previously demonstrated that acute intravenous administration of Δ^4-androstenedione for 48 hours to the preparturient monkey leads to increased maternal plasma estradiol concentrations throughout the day and an increase in nocturnal myometrial contractions.[13] The appearance of nocturnal myometrial contractions in spite of elevated maternal plasma estradiol throughout the day has been attributed to the 24-hour pattern in circulating maternal plasma oxytocin with peak concentrations occurring at night[5, 9, 23, 24] coupled with an increase in nocturnal myometrial sensitivity to oxytocin demonstrated in late-gestation monkeys and in pregnant women.[27] If the Δ^4-androstenedione treatment to the 0.8 gestation rhesus monkey is sustained, then the regularly recurring and augmenting switch from contractures to contractions occurs for several nights, accompanied by an increase in maternal estradiol concentrations, finally resulting in live delivery of the fetal rhesus monkey.[6] The current study confirms sustained elevations in maternal plasma estradiol levels after Δ^4-androstenedione treatment and reports further characterization of the model showing that the increase in maternal estradiol precedes an increase in maternal oxytocin by about 24 to 48 hours. These premature increases in maternal plasma estradiol and oxytocin after Δ^4-androstenedione treatment are of similar magnitude to the increase in estradiol[19] and oxytocin[5] measured during spontaneous term myometrial contractions in the monkey. Furthermore, the hourly changes in maternal plasma oxytocin and myometrial contractions after Δ^4-androstenedione treatment demonstrate a close association between the onset of the increase in both these variables. The daily temporal relationship between physiologic changes in maternal plasma estradiol and oxytocin and the hourly temporal relationship between plasma oxytocin and myometrial contractions are consistent with the hypothesis that estrogen-induced increases in maternal plasma oxytocin contribute to mediating both spontaneous term and Δ^4-androstenedione–induced preterm myometrial contractions.

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