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UTILIZATION OF MATERNAL AND FETAL ANDROSTENEDIONE FOR PLACENTAL ESTROGEN PRODUCTION AT MID AND LATE BABOON PREGNANCY

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Summary—The present study determined the placental and whole-body metabolism of androstenedione originating in the maternal and fetal compartments of the pregnant baboon at mid (day 100; $n = 4$) and late (day 165; $n = 3$) gestation (term = day 184) in untreated animals and at midgestation in animals ($n = 3$) treated with pellets (50 mg) of androstenedione inserted at 8-day intervals in the mother between days 70 and 100 of gestation. Baboons were anesthetized with ketamine–halothane–nitrous oxide, blood samples obtained from maternal, uterine, fetal and umbilical vessels during constant infusion of [^{3}H] or [^{14}C]androstenedione via the fetal or maternal circulation, respectively, and radiolabeled precursor/products in plasma purified by HPLC. The metabolic clearance rate (MCR; l/day/kg body wt) of androstenedione in the mother was similar at mid (81 ± 6) and late (69 ± 12) gestation and was unaltered by treatment with androstenedione (92 ± 17). Fetal MCR of androstenedione was 3-fold greater ($P < 0.05$) than in the mother and was similar in the three treatment groups. In the maternal compartment, the conversion ratio of androstenedione to estradiol (range 26–37%) exceeded ($P < 0.05$) that to testosterone (range 15–19%) which exceeded ($P < 0.05$) that to estrone (range 7–14%), a pattern unaffected by stage of gestation or treatment with androstenedione *in vivo*. Similar results were observed in the fetal compartment although values for each conversion were always 3–4-fold lower ($P < 0.05$) than in the maternal compartment. Regardless of stage of gestation or treatment with androstenedione, [^{14}C]estradiol in the uterine vein (95 ± 15 cpm/ml) exceeded ($P < 0.05$) that in the umbilical vein (3 ± 1) indicative of preferential secretion of estradiol to the maternal compartment. In contrast, the concentration of [^{14}C]estrone in uterine (15 ± 4) and umbilical (18 ± 4) vessels were similar indicating that estrone was secreted equally into the mother and fetus. Similar observations were noted for respective values for [^{3}H]estrogens derived from fetal [^{3}H]androstenedione. Placental extraction of fetal androstenedione (range 86–93%) exceeded ($P < 0.05$) that for androstenedione originating in the mother (range 44–54%) and neither were affected by stage of gestation or treatment with androstenedione *in vivo*. Less than 1% of fetal [^{3}H]androstenedione reached the maternal circulation unaltered, presumably due to placental catabolism. Similarly, the concentration of maternally-derived [^{14}C]androstenedione present in fetal plasma (<5%) was minimal. We conclude that both maternal and fetal androstenedione were extracted by the uterus and its contents and utilized almost equally for estrogen synthesis during the second half of gestation in the baboon.

INTRODUCTION

During pregnancy in humans [1], rhesus monkeys [2] and baboons [3, 4] estradiol production occurs within the placenta from androgens secreted by the maternal and fetal adrenal glands. Although dehydroepiandrosterone (DHA) and its sulfate (DHAS) are quantitatively the major androgen precursors, androstenedione, formed within the placenta from DHA via the enzyme 3β-hydroxysteroid dehydrogenase-isomerase, appears to be an obligatory intermediate [5]. In the chronically catheterized rhesus monkey near term, Walsh *et al.* [2] demonstrated that continuous infusion of a mass of androstenedione (2 mg/h) either via the fetus or mother also increased placental estrogen production. It has been suggested [6] therefore, that

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androstenedione is utilized for estrogen production approximately equally when presented to the placenta from either the maternal or fetal circulations, while DHA/DHAS is preferentially utilized from the fetal compartment. Indeed, we recently demonstrated that treatment of pregnant baboons with pellets of androstenedione inserted in the mother to deliver 15–60 mg androstenedione/day increased placental estrogen production and resulted in a physiologic distribution of estradiol and estrone into the maternal and fetal circulations, respectively [7, 8]. However, such studies cannot provide a definitive account of the normal, physiologic utilization of fetally- and maternally-derived androstenedione. In the present study, therefore, we have employed *in vivo* tracer techniques to examine the placental and whole-body metabolism of androstenedione in the maternal and fetal compartments of the pregnant baboon, with particular reference to placental estrogen formation. Specifically, the maternal and fetal metabolic clearance rates, placental extractions, and conversion ratios of maternal and fetal androstenedione to estrogens were determined at mid and late gestation. Studies were also conducted in baboons treated at midgestation with exogenous androstenedione to increase placental estrogen production in order to determine whether androstenedione dynamics were altered under conditions in which the concentrations of this estrogen precursor or estrogen itself were increased.

MATERIALS AND METHODS

Animals

Ten adult female baboons (*Papio anubis*) weighing 13–16 kg, were housed and mated as described previously [9]. Androgen dynamics were evaluated on day 100 ($n = 4$) and day 165 ($n = 3$) of gestation (term = 184 days) in untreated baboons and on day 100 of gestation in three additional animals which received androstenedione implants (50 mg each; Innovative Research Products, Toledo, OH) inserted s.c. in the mother under ketamine–HCl (Ketalar; Parke-Davis; Detroit, MI) sedation on days 70 (2 implants), 78 (4 implants), 86 (6 implants) and 94 (8 implants) of gestation. Animals were cared for and used in accordance with USDA regulations and the NIH Guide for the Care and Use of Laboratory Animals (Publication No. 85–23, 1985). The experimental protocol employed in the present study was approved by the Institutional Animal Care and Use Committee of the Eastern Virginia Medical School.

Constant infusion protocol

At 0900 h on day 100 or 165 of gestation, animals were restrained and sedated with 150 mg ketamine–HCl and catheters (C. R. Bard, Inc., Murray Hill, NJ) were inserted into a maternal saphenous vein and an antecubital vein. After i.v. administration of a priming dose of [4-^{14}C]androstenedione (0.5 μCi = 840,000 cpm/5 ml 0.9% saline–1% ethanol; sp.act. 35 mCi/mmol; New England Nuclear Corp., Boston, MA), a constant infusion (0.05 μCi = 84,420 cpm/min/0.30 ml) of [^{14}C]-androstenedione was initiated via the antecubital vein while a solution of 5% dextrose–water containing 5 mg/ml ketamine was infused (1.0 ml/min) via the saphenous vein to maintain sedation. Baboons were then intubated and anesthesia with halothane–nitrous oxide [7] initiated. After a 15 min equilibration period, a laparotomy and hysterotomy was performed and a fetal femoral vein cannulated with a 25-gauge infusion set (Abbott Hospitals, Inc., Chicago, IL) as previously described [10]. A priming dose of [1 α,2 α-^{3}H]androstenedione (0.9 μCi = 912,000 cpm; sp.act. 51 Ci/mmol; NEN) in 0.5 ml saline–1% ethanol was then administered, and a constant infusion of [^{3}H]androstenedione (0.18 μCi = 182,252 cpm/min/0.1 ml) begun. Blood samples (7–10 ml) were collected in EDTA-tubes (Baxter, Columbia, MD) obtained from the maternal saphenous vein and right and left uterine veins 50, 60 and 70 min after onset of isotope infusion into the fetus. At 70 min, blood samples were also collected from the contralateral fetal femoral vein (0.7–1.0 ml) and from the umbilical artery and vein (1.0–2.0 ml). All blood samples were kept on ice and plasma, separated by centrifugation at 3000 rpm (4°C), and stored at −20°C until analyzed.

Analyses

Plasma samples (0.3–3.0 ml) were extracted with diethyl ether after addition of 20 μg each of radioinert androstenedione, testosterone, estradiol, and estrone. Solvents were evaporated under nitrogen and steroids reconstituted in 6 ml methanol–water (2:1). Extracts were applied to a Waters C18 Sep Pak (Millipore Corp., Millford, MA) pre-wetted with absolute

methanol and washed sequentially with 2 ml water, 1 ml 10% methanol in water and 2 ml 20% acetone in water. Steroids were then eluted with 5 ml absolute methanol, solvent evaporated, and contents, reconstituted in 20 μl HPLC-grade methanol (Baxter; Columbia, MD), applied to a 4.6 mm (i.d.) × 25 cm Ultrasphere column (Beckman, Columbia, MD) for purification by HPLC (Beckman). Steroids were eluted with HPLC grade tetrahydrofuran–methanol–water (35:35:30; changed to 45:45:10 over a 1 min gradient after 12 min; flow rate 1 ml/min). Purified fractions (androstenedione, RT = 19 min; testosterone, RT = 21 min; estrone, RT = 29 min; estradiol, RT = 32 min) were collected using a Foxy Fraction Collector (ISCO Inc., Lincoln, NB) and radioactivity determined by liquid scintillation spectrometry using a Beckman LS 8000 with automatic external quench correction for efficiency ([^{3}H] = 46%; [^{14}C] = 76%) and for contributions of ^{14}C (19.8%) into the ^{3}H channel and of ^{3}H (<0.1%) into the ^{14}C channel [11]. Samples which included blank vials, were counted for 200 min or until a counting error of ⩽2% was achieved in both the ^{3}H and ^{14}C channels. Recovery (range 50–75%) was estimated using a Beckman Integrator whereby peak areas in unknown samples were compared to those elicited by standard hormone concentrations (2–20 μg). Purity (>95%) of isolated fractions was confirmed in selected experiments by recrystallization with acetone–methanol. Radioisotopic content of various fractions were applied to the formulas of Tait and Burstein [12], Horton and Tait [13], and Baird *et al.* [14] to calculate the maternal and fetal: metabolic clearance rates (MCR) of androstenedione (MCR = cpm androstenedione infused per day/cpm androstenedione·liter peripheral plasma), the conversion ratio of androstenedione to estradiol, estrone, and testosterone (cpm product/cpm androstenedione), and the percentage extraction of androstenedione by the uterus and its contents (1 minus: cpm androstenedione in umbilical vein or uterine vein/cpm androstenedione in umbilical artery or maternal saphenous vein).

RESULTS

Table 1 depicts representative experimental data used to calculate androstenedione metabolic parameters in the maternal compartment at midgestation in one baboon. There was no significant difference in the counts per min/ml of [^{3}H] or [^{14}C]androstenedione in maternal saphenous serum at 50, 60 and 70 min, indicating that radioisotopic equilibrium was apparently achieved in the maternal and presumably in the fetal compartment using the constant infusion protocol outlined in the Materials and Methods. Because of the volume of plasma required to determine isotopic content in the fetal blood, only single fetal saphenous and umbilical samples were obtained during the infusion to ensure that cardiovascular dynamics were not compromised. However, the ^{3}H/^{14}C concentrations of estradiol and estrone in maternal blood at these three time periods were also fairly stable supporting our suggestion that data were obtained under conditions of isotopic equilibrium in the fetal and maternal compartments. In the subsequent tables and figures, data for metabolic parameters in the mother reflect the average for values calculated at 50, 60 and 70 min, whereas those for the fetus represent single point determinations.

In previous studies [7, 8], we reported that maternal serum estradiol concentrations at midgestation (0.7 ± 0.2 ng/ml) were increased 3-fold at late gestation (1.8 ± 0.1 ng/ml) and

Table 1. Representative maternal serum concentrations (counts per min/ml) of [^{3}H]/[^{14}C]androstenedione, estradiol, and estrone after constant i.v. infusion of [^{3}H]androstenedione to the fetus and [^{14}C]androstenedione to the mother in one pregnant baboon at midgestation[a]

	Androstenedione		Estradiol		Estrone	
Time (min)	[^{3}H]	[^{14}C]	[^{3}H]	[^{14}C]	[^{3}H]	[^{14}C]
50	28	164	127	23	16	9
60	24	178	138	21	17	7
70	27	183	128	23	19	8
Mean ± SD[b]	26 ± 2	175 ± 10	131 ± 6	22 ± 1	17 ± 2	8 ± 1
% CV[c]	7.9	5.6	4.6	5.2	8.8	7.5

[a]The baboon was constantly infused with [^{14}C]androstenedione via a maternal antecubital vein and [^{3}H]androstenedione via a fetal femoral vein. Blood samples were obtained from a maternal saphenous vein 50, 60 and 70 min after onset of isotope infusion to the fetus.

[b]Mean ± standard deviation; [c]Coefficient of variation.

Table 2. MCR of androstenedione (Δ^4A) in maternal and fetal compartments of the baboon at mid and late gestation and following androstenedione treatment at midgestation[a]

	Maternal		Fetal	
	l/day	l/day/kg body wt	l/day	l/day/kg body wt
Mid	1101 ± 77	81 ± 6	47 ± 7[c]	235 ± 33[c]
Mid + Δ^4A[b]	1285 ± 243	92 ± 17	47 ± 8[c]	238 ± 42[c]
Late	980 ± 124	69 ± 12	149 ± 26[cd]	186 ± 33[c]

[a]Baboons infused with [^{3}H] or [^{14}C]androstenedione via the fetal and maternal circulation, respectively, at mid (day 100; $n = 4$) or late (day 165; $n = 3$) gestation (term = day 184). MCR = cpm androstenedione infused·day/cpm androstenedione·liter peripheral plasma.

[b]Animals ($n = 3$) treated with increasing numbers of androstenedione pellets (50 mg) inserted s.c. in the mother between days 70 and 100 of gestation.

[c]Different ($P < 0.05$; paired "t" test) from respective mean (±SE) value in the mother.

[d]Greater than values at midgestation ($P < 0.05$, Analysis of Variance).

4-fold by treatment with androstenedione at midgestation (2.4 ± 0.3 ng/ml). In the baboon, maternal androstenedione concentrations are similar at mid and late gestation, averaging 0.4 ± 0.1 ng/ml, and are lower than the respective value (5 ng/ml) in the fetus at midgestation [8]. Treatment of the mother with androstenedione did not increase fetal androstenedione concentrations, but did increase maternal levels by approx. 10-fold (data not shown).

The MCR of androstenedione in the mother was similar at mid and late gestation and was unaltered by treatment with androstenedione *in vivo* at midgestation (Table 2). In contrast, the MCR of androstenedione in the fetus was greater ($P < 0.05$) at term than at midgestation. However, this difference was not apparent when the MCR was expressed per kg fetal body wt. When expressed per kg body wt, the MCR of androstenedione in the fetus exceeded ($P < 0.05$) that in the mother.

Part of the metabolism of androstenedione in the maternal compartment can be accounted for by conversion to estradiol, estrone and testosterone (Table 3). The conversion ratio of androstenedione to estradiol (range 26–37%) exceeded ($P < 0.05$; Analysis of Variance) that to testosterone (range 15–19%), which exceeded ($P < 0.05$) that to estrone (range 7–14%). This pattern of conversion was not affected by stage of gestation or treatment with androstenedione *in vivo*. Similar results were observed in the fetal compartment, although values for each conversion were always lower ($P < 0.05$; paired "t" tests) than respective conversion in the maternal compartment.

The concentrations of [^{14}C]estradiol and [^{14}C]estrone in uterine and umbilical vein plasma were not influenced by stage of gestation or by androstenedione treatment at midgestation. Therefore, overall mean values for the three treatment groups were combined and are presented in Fig. 1. The uterus (e.g. the placenta) appeared to be a major site of estrogen formation with estradiol being secreted preferentially into the uterine vein (to the mother) and estrone equally into the uterine and umbilical vein (to the fetus). Similar observations were noted for respective values for [^{3}H]estrogens derived from fetal [^{3}H]androstenedione (data not shown).

Table 3. Conversion ratio (mean ± SE) of androstenedione to estradiol, estrone and testosterone in the baboon mother and fetus at mid and late gestation[a]

	$\Delta^4A \rightarrow E_2$		$\Delta^4A \rightarrow E_1$		$\Delta^4A \rightarrow T$	
	Maternal	Fetal	Maternal	Fetal	Maternal	Fetal
Mid	30 ± 9[b]	8 ± 3[c]	7 ± 1[b]	3 ± 1	18 ± 3[b]	4 ± 1
Mid + Δ^4A	26 ± 3[b]	5 ± 1	8 ± 1[b]	1 ± 1	15 ± 2[b]	3 ± 1
Late	37 ± 9[b]	13 ± 7	14 ± 3[b]	3 ± 1	19 ± 3[b]	8 ± 2

[a]Animals infused with [^{3}H]/[^{14}C]androstenedione via fetal/maternal circulation, respectively on day 100 (Mid; $n = 4$), day 165 (Late; $n = 3$) or day 100 following maternal treatment with androstenedione ($n = 3$). See legend to Table 2 for details. Conversion ratio calculated as cpm product·ml peripheral plasma/cpm androstenedione·ml peripheral plasma and expressed as a percentage (e.g. ratio × 100).

[b]Greater ($P < 0.05$; paired "t" test) than respective values in the fetus. Regardless of time of gestation, in the maternal compartment, the mean value for the conversion of $\Delta^4A \rightarrow E_2$ was greater than that for conversion of $\Delta^4A \rightarrow T$ which exceeded conversion of $\Delta^4A \rightarrow E_1$ ($P < 0.05$; Analysis of Variance).

[c]In the fetal compartment, regardless of the time of gestation, the mean value for the conversion of $\Delta^4A \rightarrow E_2$ was geater than that for conversion of $\Delta^4A \rightarrow E_1$ ($P < 0.05$; Analysis of Variance) which was similar to the conversion of $\Delta^4A \rightarrow T$.

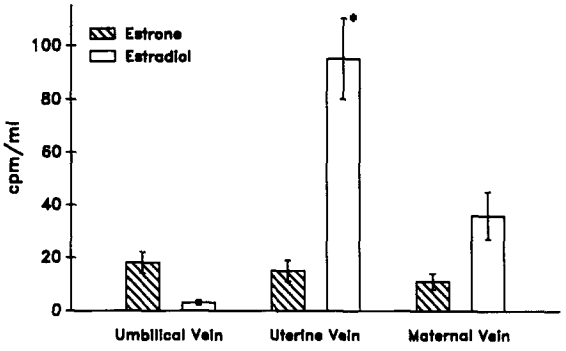

Fig. 1. Plasma concentrations (cpm/ml) of [^{14}C]estradiol and [^{14}C]estrone in umbilical, uterine and maternal venous blood samples obtained from baboons infused with [^{14}C]androstenedione via a maternal antecubital vein on day 100 ($n = 4$), day 165 ($n = 3$) or day 100 following maternal treatment with androstenedione ($n = 3$). See legend of Table 2 for details. Because radiolabeled estrogen concentrations were not influenced by stage of gestation or by androstenedione treatment, individual values ($n = 10$) for the three treatment groups were pooled and are presented as the overall mean ± SE. The asterisk indicates that the mean value in uterine vein differs from that in the maternal and umbilical vein ($P < 0.05$; Analysis of Variance).

As outlined in Fig. 2, there was extensive extraction of fetal androstenedione by the placenta, and of maternal androstenedione by the uterus and its contents, presumably reflecting primarily placental extraction. Moreover, fractional extraction of fetal androstenedione was greater ($P < 0.05$) than that for androstenedione originating in the mother. Placental extraction was not affected by time of gestation or

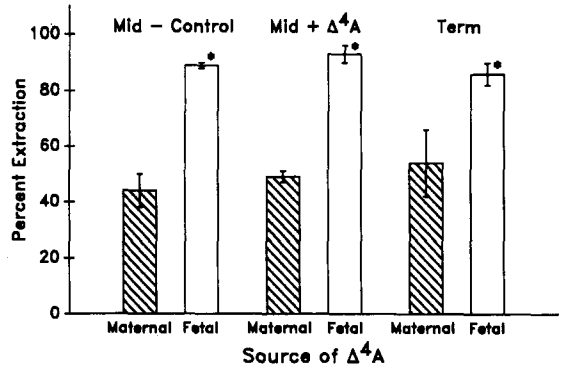

Fig. 2. Placental extraction of [^{3}H]androstenedione and [^{14}C]androstenedione infused via the fetal and maternal circulation, respectively on day 100 (Mid; $n = 4$) and day 165 (Term; $n = 3$) in untreated baboons and on day 100 following maternal treatment with androstenedione. Extraction of fetal androstenedione = 1—(cpm androstenedione·ml umbilical venous plasma/cpm androstenedione·ml umbilical arterial plasma) × 100. Extraction of maternal androstenedione = 1—(cpm androstenedione·ml uterine venous plasma/cpm androstenedione·ml maternal saphenous venous plasma) × 100. Asterisk indicates that the mean (±SE) placental extraction of fetal androstenedione exceeds that for androstenedione originating in the maternal compartment ($P < 0.05$; paired "t" test).

Table 4. Concentrations of [^{3}H]/[^{14}C]androstenedione (cpm/ml) in maternal and fetal serum following infusion of [^{3}H]androstenedione to the fetus and [^{14}C]androstenedione to the mother at mid and late baboon gestation[a]

	[^{3}H]Δ^{4}A		[^{14}C]Δ^{4}A	
	Maternal	Fetal	Maternal	Fetal
Mid	15 ± 5	5183 ± 1560	112 ± 25	4 ± 2
Mid + Δ^{4}A	12 ± 5	6025 ± 1531	82 ± 11	3 ± 2
Late	22 ± 6	2350 ± 427	142 ± 28	6 ± 2

[a]See legend to Tables 2 and 3 for details. Values = Mean ± SE.

treatment with androstenedione *in vivo*. Despite the very high placental extraction of fetal [^{3}H]androstenedione, very little of this labeled hormone reached the maternal circulation unaltered (Table 4), presumably due to placental metabolism. Similarly, the concentration of maternally-derived [^{14}C]androstenedione present in fetal plasma was minimal (Table 4).

DISCUSSION

The present results demonstrate that both maternal and fetal androstenedione were extracted by the uterus and its contents (e.g. the placenta) and were utilized for estrogen synthesis during the second half of gestation in the baboon. Moreover, placental extraction of androstenedione appeared to be almost complete when presented to the uterus from the fetal compartment and was significantly more extensive than extraction of maternal androstenedione. The latter was not due to isotopic dilution by non-radiolabeled hormone, because endogenous concentrations of androstenedione in the fetus exceed those in the maternal circulation of the baboon [8] as in the rhesus monkey [15, 16] and human [17]. Furthermore, placental extraction of maternal radiolabeled androstenedione was not decreased at midgestation in animals treated with exogenous androstenedione. Despite the high extraction of fetal androstenedione by the placenta, very little reached the maternal circulation. This suggests that fetal androstenedione was extensively metabolized following placental uptake. It also implies that the difference in relative rates of androstenedione extraction from the fetal and maternal sides cannot be accounted for by net transplacental transfer favoring fetus to mother. It is known, however, that the uterine vein drains blood from the myometrium and decidua as well as the placenta [18], whereas the umbilical vein drains only the placenta. Therefore, the higher extraction of fetal androstenedione may simply reflect this difference in the

specific tissues drained by the sample vessels. This would imply, therefore, that myometrial/decidual metabolism of androstenedione is minimal, consistent with previous reports *in vitro* [19] and thus would contribute quantitatively very little to circulating estrogen concentrations.

Placental extraction of androstenedione appears to contribute quantitatively to the overall metabolic clearance rate of this hormone in both the maternal and fetal circulation. Assuming that 5–8% of the cardiac output reaches the uterus as has been demonstrated in the near-term pregnant rhesus monkey [18, 20], it is estimated that uterine blood flow would approximate 335 l/day during baboon pregnancy. With a mean extraction of 50% and an hematocrit of 0.4, we calculate that uterine clearance of maternal androstenedione approximates 67 l/day. Since the overall clearance of androstenedione in the maternal compartment averaged 1040 l/day at mid and late gestation, uterine extraction of androstenedione could account for as much as 6% of the whole body metabolic clearance of androstenedione during pregnancy. Edman *et al.* [21] estimated, using the constant infusion technique, that approx. 10% of maternal plasma androstenedione was cleared by the placenta during gestation in humans. Umbilical blood flow in the baboon between days 150–160 of gestation approximates 80 ml/min or 115 l/day [22]. Therefore, we estimate that placental clearance of fetal androstenedione (90% extraction × 0.4 hematocrit × 115 l/day flow) approximates 41 l/day. At term, the total metabolic clearance rate of androstenedione by the fetus is 149 l/day. Therefore, it appears that placental metabolism could account for as much as 28% of the clearance of androstenedione in the baboon fetus at this time in gestation. In addition to formation of estrogen, such a high placental clearance may act to ensure removal of this relatively weak androgen from the fetus and to prevent its ultimate conversion within the fetus to more potent androgens such as testosterone and subsequently dihydrotestosterone. Indeed, the fetal monkey liver has abundant quantities of the enzyme 17β-hydroxysteroid dehydrogenase [23]. Thus, despite the likely high enzyme activity in the fetal baboon, the mean conversion ratio of androstenedione to testosterone (4–8%) was significantly lower than that measured in the maternal circulation (15–19%).

Although the quantitative contribution of placental clearance to the whole body MCR of androstenedione in the mother is lower than in the fetus, this does not imply that placental metabolism of maternal hormone is less important physiologically than is metabolism of fetal hormone. Thus, the present study demonstrated that radiolabeled androstenedione of maternal origin did not reach the fetal circulation in appreciable quantities even in animals supplemented with radioinert androstenedione. Therefore, we suggest that the fetus is normally protected from androgens in the maternal circulation by placental metabolism of maternal hormone. Recently, Resko *et al.* [16] demonstrated that treatment of pregnant rhesus mothers with pharmacologic doses of testosterone propionate for 10 days at midgestation did not increase testosterone or DHT concentrations in the fetus of control males, but did increase maternal testosterone concentrations from 0.5 to over 120 ng/ml and maternal androstenedione from 0.3 to 6.5 ng/ml. Although fetal androstenedione concentrations were elevated in steroid-treated monkeys, it would appear that placental metabolism as well as fetal androgen catabolism via fetal hepatic 17β-hydroxysteroid dehydrogenase activity[23] provide the major mechanisms to protect the fetus from excess testosterone production in the mother.

The results of the present study also demonstrate that the conversion ratio of androstenedione to estradiol exceeded that for conversion to estrone and was similar at mid and late gestation. Moreover, despite an increase in exogenous androstenedione, conversion remained unchanged accounting for the marked elevation in maternal estradiol concentrations previously measured [7, 8] in androstenedione-treated animals. Therefore, it appears that placental aromatase may not be a rate-limiting enzyme in the baboon placenta for estrogen synthesis, as suggested in the human placenta (for review see [4]). Rather, the availability of androgen precursors [24] and the rate of uteroplacental blood flow [25, 26] may be more important determinants of estrogen production rates. Thus, factors regulating fetal and/or maternal adrenal androgen secretion during primate pregnancy will also influence placental estrogen secretion. Estrogen may also participate in regulating its own production. Thus, we [27] demonstrated that a negative feedback system may be operative during early to midgestation in the baboon in which placental estrogen acts to

block ACTH-stimulated fetal adrenal DHA production.

Our present study also demonstrated that estradiol formed either from maternal or fetal androstenedione is secreted preferentially into the maternal circulation, whereas estrone is secreted into both compartments. These results are consistent with those of Gurpide *et al.* [28] in the human and Walsh and McCarthy [29] in the monkey demonstrating, either *in vitro* or *in vivo*, selective placental secretion of radiolabeled estradiol and estrone to the maternal and fetal compartments, respectively. In the present study, the pattern of placental estrogen secretion accounts, in part, for the greater conversion ratio of androstenedione to estradiol in the maternal versus the fetal compartment. Thus, we suggest that although the conversion ratio of maternal androstenedione to total estradiol exceeds that in the fetus, the quantitative contribution of maternal and fetal derived androstenedione to estradiol production are probably similar. The latter is, most likely, also true for the production of estrone. Indeed, employing mean endogenous concentrations for maternal and fetal estrogens and androstenedione measured previously at midgestation in the baboon [8, 10] to determine steroid specific activities, we calculate, using the formulas of Gurpide [30], that at midgestation $3.3 \pm 0.9\%$ of maternal estradiol and $2.7 \pm 0.9\%$ of maternal estrone is derived from maternal androstenedione while $5.5 \pm 1.8\%$ of the estradiol and $2.2 \pm 0.9\%$ of the estrone in the mother is derived from androstenedione of fetal origin. Thus, we conclude that maternal and fetal androstenedione are utilized equally by the baboon placenta for estrogen production as has been suggested by Walsh [6] in the monkey. In humans, more than 80% of the estradiol produced during mid to late gestation is derived from DHAS produced by the maternal and fetal adrenal glands [31]. The same is apparently true in the baboon in which it has been shown that DHA and DHAS of maternal [32] and fetal origin [3, 33] are quantitatively the primary androgens utilized for placental estrogen production. The results of the present study are consistent with the latter observations since the quantitative contribution of androstenedione to placental estrogen production ($< 10\%$) appears relatively minor.

The pattern of androgen metabolism measured in the maternal compartment of the baboon compares favorably to that in the pregnant human [21, 34]. Thus, the MCR of androstenedione in the baboon (1040 l/day or 86 l/day/kg) is of the same order of magnitude as in the human (2827 l/day; or 47 l/day/kg with body wt estimated at 60 kg). Moreover, the conversion ratio of androstenedione to estradiol (0.19–0.49) at mid to late gestation in humans [34] compares favorably to the conversion ratio (0.30–0.37) measured in baboons of the present study. Similarly, the conversion ratio of androstenedione to estrone in human pregnancy (0.04; [34]) also compares favorably to that (0.07–0.14) measured in the pregnant baboon. In addition, because the MCR of estradiol in the baboon (450 l/day; Pepe and Albrecht unpublished observations) is approx. 50% of that for androstenedione, the estimated transfer constant (conversion ratio × MCR estradiol/MCR androstenedione) for maternal androstenedione to estradiol in baboons of the present study would approx. 0.17, a value similar to that (0.18) measured in late gestation in humans [21]. Finally, the conversion ratio of androstenedione to testosterone in the non-pregnant (0.14; [13]) and pregnant (0.20) human is almost identical to that (0.18) measured in the present study in pregnant baboons. Collectively these findings plus those on placental estrogen formation and preferential secretion of estradiol into the maternal compartment and estrone into the fetus further support the hypothesis that the baboon provides an excellent model for studies of the regulation of fetoplacental function.

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