Transplacental Passage and Fetal Secretion of Aldosterone

FRANCIS BAYARD, ISADORE G. ANCES, ALAN J. TAPPER, VIRGINIA V. WELDON, AVINOAM KOWARSKI, and CLAUDE J. MIGEON

From the Harriet Lane Service of the Children's Medical and Surgical Center, and the Department of Obstetrics and Gynecology, The Johns Hopkins Hospital and University, Baltimore, Maryland 21205; and from the Department of Obstetrics and Gynecology of the University of Maryland, School of Medicine, Baltimore, Maryland 21201

ABSTRACT The transplacental passage and the production of aldosterone were studied in late pregnancy during a constant infusion of 1,2-aldosterone-3H to mothers at the time of elective cesarean section.

It was found that, while maternal aldosterone crossed the placenta, there was a significant secretion of aldosterone by the fetus. The aldosterone concentration in fetal plasma was 2–12 times higher than that of the corresponding mothers.

Pregnancy had no effect on the metabolic clearance rate of aldosterone, but it increased the rate of production of this steroid. However, the increments that we observed were smaller than those reported in previous reports. The discrepancy was probably due to differences in body posture, our subjects being supine for at least 10 hr at the time of study.

INTRODUCTION

A well defined adrenal cortex has been observed in the human fetus early in pregnancy, and aldosterone has been isolated from fetal adrenal glands (1). However, it is not known whether this steroid is secreted before delivery.

In newborn infants, aldosterone secretion rate is lower during the first few days of life than later on (2). These results may be interpreted as suggesting a lack of aldosterone secretion by the fetus with a sluggish start of secretion after delivery. Another explanation is that the low secretion in the immediate postnatal period is secondary to water and electrolyte retention during fetal life due to elevated levels of aldosterone secreted by the fetus or originating from the mother.

The purpose of this study was to investigate whether maternal aldosterone can cross the placenta and whether the fetus secretes its own steroid.

METHODS

Subjects. 11 normal pregnant women, ranging in age from 15 to 38 yr were studied. Patients 1 and 2 underwent hysterotomy for psychiatric reasons at the 20th wk of pregnancy. Patients 3–11 underwent an elective cesarean section at 38–40 wk gestation. All pregnancies had been normal; the placentas and the newborn infants (two boys and nine girls) were also normal. The patients were hospitalized 1 day before surgery. The diet was unrestricted, except for patient 11, who was ordered to have a low sodium diet by her physician because of a slight degree of proteinuria. The patients remained in their beds and received no food from 9 p.m. to the time of surgery the following morning.

The experimental project was reviewed and approved by the Committees on Clinical Investigation and the Committees on Radiation Control of The Johns Hopkins University and the University of Maryland. Informed consent was obtained from all subjects studied.

Experimental design. 50 ml of blood was drawn in heparinized syringes from the mothers between 6 and 8:30 a.m. An IV infusion of 5 μCi of 1,2-3H-aldosterone (specific activity, 34 Ci/mmol) diluted in 40–50 ml of 5% glucose solution was then started, using a constant infusion pump (Harvard Apparatus Co., Millis, Mass.). The rate of infusion was 2.9 ml/min during the 1st min and 0.145 ml/min for the remaining time of the experiment. Four heparinized blood samples (10 ml each) were drawn from the opposite arm at 10–20-min intervals beginning 105 min after the start of the experiment. A fifth sample was drawn at the moment of delivery, about 10–20 min after the preceding sample. Fetal blood was drawn at the same time from the cord vein.

The rate of 1,2-aldosterone-3H infusion was determined by collecting three 2-min effluxes from the constant infusion pump immediately after removing the needle from the mother's arm.

Subjects 9 and 10 did not receive the infusion and only a blood sample was collected from mother and cord at the moment of delivery.

Methods. After centrifugation and plasma separation, all
samples were frozen until analyzed. The concentrations of 1,2-aldosterone-4H in maternal and fetal plasma were determined as follows: 4-aldosterone-4C was added as an indicator for losses; after extraction and acetylation with non-radioactive acetic anhydride, aldosterone diacetate was purified by paper chromatography (cyclohexane: benzene: methanol: water, 100:40:100:20); and finally the 4H/4C ratio was determined. Each sample was counted in a liquid scintillation counter for 200 min.

Plasma aldosterone concentration was determined using a double isotope derivative method previously described (3). A correction for the 1,2-aldosterone-4H in the fetal plasma was applied (4). The plasma values after the last purification stage of the method were corrected for the mean value of two water blanks measured at the same time as the samples (the blank values ranged from 0 to 0.2 muppy).

**Theoretical model.** The theoretical model in this study is the same as that used previously for the investigation of fetal and maternal secretion of cortisol and placental resistance in pregnant sheep (5). The only difference is that, in the present experiment, the fetus was not infused with radioactive steroid. Calculation of the metabolic clearance rate (MCR) of aldosterone in the maternal compartment in liters/day was carried out using the following formula:

\[
\text{MCR} = \frac{\text{rate of infusion of 1,2-aldosterone-4H (cpm/day)}}{\text{plateau of 1,2-aldosterone-4H (cpm/liter) in mother}}
\]

The blood production (\(\mu g/24 \text{ hr}\)) in the maternal compartment was calculated as MCR (liters/24 hr) \(\times\) maternal plasma aldosterone (pg/liter). It should be borne in mind that the blood production of the mother, calculated as described above, represents the maternal secretion plus the net transfer of fetal steroid into the maternal compartment.

Because of the conditions of our study, it was impossible to obtain more than one sample of fetal blood. Therefore, we cannot prove that the concentration of 1,2-aldosterone-4H had reached a plateau and that equilibrium was present in the fetal compartment. Theoretically, a plateau of 1,2-aldosterone-4H in the maternal compartment should be proof of equilibrium in all compartments including the fetus. The rates of transfer could, however, be so slow and/or so small that they would not affect appreciably the radioactive plateau in the mother. Previous studies with cortisol and other steroids have shown that the transplacental passage of these compounds is not slow and therefore it is reasonable to assume equilibrium in all compartments after 2 hr of constant infusion (6).

### RESULTS

**MCR determination.** In the nine cases studied, a constant concentration of 1,2-aldosterone-4H was obtained after 105 min of constant infusion, allowing the calculation of the MCR as shown in Table I. The missing values in the table are the result of either lack of sample collection or technical errors. Individual levels were less than 20% different from the mean. The MCR (mean ± 1 sp) under these conditions was 1789 ± 517 liters/day. The values for the two patients at 20 wk of pregnancy (subjects 1 and 2) were within the range observed in the seven mothers near term.

**Concentration of 1,2-aldosterone-4H in maternal and fetal plasma.** Table II shows that there is transplacental passage of aldosterone. The fetal plasma levels of 1,2-aldosterone-4H expressed as percentage of the maternal values ranged from 40.0 to 123.7% with a mean of 73.4%. We could not detect a difference in the results at 20 wk of pregnancy (subjects 1 and 2) and at term.

**Concentration of aldosterone in maternal and fetal plasma.** Table II summarizes the results obtained in seven mothers and six fetuses. It must be noted that, except for subject 11, all patients were on an ad lib Na diet and in supine position for at least 10 hr. Under these conditions, and excluding patient 11, the mean plasma aldosterone concentration in the mothers was

### TABLE I

**Metabolic Clearance Rate of Aldosterone during Pregnancy**

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Age</th>
<th>105 min</th>
<th>120 min</th>
<th>130 min</th>
<th>140 min</th>
<th>150 min</th>
<th>Mean</th>
<th>Rate of Infusion (cpm/liter)</th>
<th>MCR (liters/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>21,190</td>
<td>17,290</td>
<td>—</td>
<td>19,840</td>
<td>20,840</td>
<td>19,700</td>
<td>33,575</td>
<td>1,696</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>20,410</td>
<td>21,530</td>
<td>22,980</td>
<td>—</td>
<td>21,600</td>
<td>55,944</td>
<td>2,584</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>14,500</td>
<td>15,400</td>
<td>15,400</td>
<td>—</td>
<td>15,000</td>
<td>35,592</td>
<td>2,380</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>12,780</td>
<td>13,000</td>
<td>12,800</td>
<td>—</td>
<td>13,500</td>
<td>13,000</td>
<td>12,523</td>
<td>964</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>8,850</td>
<td>8,200</td>
<td>8,330</td>
<td>7,400</td>
<td>8,200</td>
<td>12,929</td>
<td>1,578</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>9,140</td>
<td>8,200</td>
<td>—</td>
<td>8,150</td>
<td>7,700</td>
<td>8,290</td>
<td>16,560</td>
<td>1,994</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>10,500</td>
<td>13,300</td>
<td>12,200</td>
<td>13,500</td>
<td>11,400</td>
<td>12,200</td>
<td>14,436</td>
<td>1,182</td>
</tr>
<tr>
<td>8</td>
<td>18</td>
<td>12,750</td>
<td>12,100</td>
<td>13,100</td>
<td>13,700</td>
<td>13,300</td>
<td>13,000</td>
<td>23,983</td>
<td>1,845</td>
</tr>
<tr>
<td>11*</td>
<td>21</td>
<td>11,550</td>
<td>8,230</td>
<td>9,070</td>
<td>8,500</td>
<td>9,300</td>
<td>17,611</td>
<td>1,880</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SD 1,789 ± 516

* Patient on restricted Na diet.
3.7 ± 1.4 μg/100 ml. Subject 11 who was on a restricted sodium diet showed a considerable increase of the plasma aldosterone concentration.

The concentration of aldosterone in plasma was measured only in fetuses near term. In all cases, it was greater than that of the corresponding mother. Since we found a reverse relationship for 1,2-aldosterone-5H concentrations, the specific activities of aldosterone in fetal plasma (cpm/mag) represented 6.5–23.4% of those of the mothers. The aldosterone concentration of the infant born of the mother on low Na diet (case 11) was also markedly elevated.

**Blood production of aldosterone by the mothers.** Knowledge of both MCR and plasma concentrations has allowed the calculation of the blood production rate of aldosterone in five mothers near term (Table III). Four mothers on an ad lib. Na diet had a mean production rate of 63.7 μg/24 hr, while the mother under low Na diet had a production of 553 μg.

**DISCUSSION**

**MCR of aldosterone in the mothers.** Our results are in agreement with those of Tait, Little, Tait, and Flood (7), who found a mean ±1 SD of 1543 ±113 liters/24 hr in pregnant women at term. These values also are similar to those observed in nonpregnant women (7).

**Transplacental passage of aldosterone.** Our findings demonstrate that 1,2-aldosterone-5H administered to the mother crosses the placenta. However, maternal concentrations are slightly higher than those of the fetus. Unlike cortisol, aldosterone does not have a specific plasma binding protein and is loosely bound to proteins in blood. Furthermore, its binding to plasma proteins does not increase during pregnancy (8). Therefore the difference in maternal and fetal concentrations of 1,2-

**aldosterone-5H cannot be accounted for by changes in binding of the steroid. It could be the result of a placental resistance of sufficient magnitude to prevent achievement of equilibrium in the time allotted. Alternatively, the difference in 1,2-aldosterone-5H concentration could be due to the fact that the fetus is metabolizing maternal aldosterone at an appreciable rate relative to its transplacental flux. We must also consider the possibility of an active transport of aldosterone toward the maternal side if the 1,2-aldosterone-5H was in equilibrium in the maternal-placental-fetal unit.**

**Production of aldosterone in the fetus.** In contrast to the concentration of 1,2-aldosterone-5H, the levels of endogenous aldosterone were consistently higher in the fetus, resulting in specific activities which were much lower on the fetal side. If one assumes that the values of radioactive and nonisotopic aldosterone determined in this study were obtained when equilibrium was reached on both sides of the placenta, then it must be

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**Table II**

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Aldosterone in maternal plasma</th>
<th>Aldosterone in fetal plasma</th>
<th>(Fetal/maternal) X 100</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cpm/100 ml</td>
<td>mg/100 ml</td>
<td>SA</td>
</tr>
<tr>
<td>1</td>
<td>1,970</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>2,160</td>
<td>4.7</td>
<td>459</td>
</tr>
<tr>
<td>3</td>
<td>1,500</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>1,300</td>
<td>1.7</td>
<td>765</td>
</tr>
<tr>
<td>5</td>
<td>820</td>
<td>2.0</td>
<td>410</td>
</tr>
<tr>
<td>7</td>
<td>1,220</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>1,300</td>
<td>4.6</td>
<td>283</td>
</tr>
<tr>
<td>9</td>
<td>—</td>
<td>5.0</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>—</td>
<td>4.4</td>
<td>—</td>
</tr>
</tbody>
</table>

Mean ±SD: 3.7 ± 1.4

11

Mean ±SD: 17.2 ± 7.5

* Patient on restricted Na diet.

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**Table III**

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>MCR</th>
<th>Plasma aldosterone</th>
<th>Blood production rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>liters/day</td>
<td>mg/100 ml</td>
<td>μg/day</td>
</tr>
<tr>
<td>2</td>
<td>2584</td>
<td>4.7</td>
<td>121</td>
</tr>
<tr>
<td>4</td>
<td>964</td>
<td>1.7</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>1,178</td>
<td>2.0</td>
<td>32</td>
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<tr>
<td>8</td>
<td>1,845</td>
<td>4.6</td>
<td>85</td>
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<tr>
<td>9</td>
<td>1,780</td>
<td>5.0</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>1,780</td>
<td>4.4</td>
<td>79</td>
</tr>
</tbody>
</table>

Mean ±SD: 3.7 ± 1.4

11

Mean MCR of nine mothers.

† Subject on restricted Na diet.
concluded that the fetus secreted aldosterone. This conclusion is in accordance with the demonstration that the human fetal adrenal cortex is capable of converting progesterone to aldosterone in vitro (9, 10). The fetus of the pregnant ewe has also been shown to secrete aldosterone (11).

In a previous study of cortisol secretion during pregnancy in sheep (5), the ratio of maternal and fetal MCR was similar to the ratio of their respective body weights. In some aspects, cortisol metabolism in sheep is comparable to aldosterone metabolism in humans with both steroids having low protein binding and high MCR. Although analogies about different species may be very erroneous, one may assume that the ratio of MCR of aldosterone in the mother and her fetus is related to their respective body weights, and then one can obtain a rough approximation of the fetal production rate of aldosterone at term. Postulating that the MCR of aldosterone in the fetus at the time of birth is about one-twentieth that of the mother, the estimated blood production rate of the fetus would be in the range of 15 μg/24 hr, using a mean fetal plasma concentration of aldosterone of 17.2 μg/100 ml. This value agrees fairly well with the values reported by Weldon, Kowarski, and Migeon (2). In spite of this low aldosterone secretion rate, the fetus at term has high plasma aldosterone levels. Further studies will be required to elucidate the relationship between water-electrolyte metabolism and aldosterone levels during the neonatal period.

The present study has demonstrated that both mother and fetus secrete aldosterone, and therefore represent two pools with secretion and metabolism in both. An error of unknown magnitude is therefore introduced in all estimations of aldosterone production rates during pregnancy by the urinary metabolite isotopic dilution method (12).

**Plasma aldosterone concentration and blood production rate in the mother.** We have found that the mean concentration of aldosterone in maternal plasma obtained in the morning to be only twice higher than the values reported by Balikian, Brodie, Dale, Melby, and Tait (4) in 16 normal subjects under similar conditions (ad lib. Na diet and supine position, mean ± 1 SD, 1.9 ±1.04 μg/100 ml). Our blood production rates (Table III) fell within or were somewhat higher than the normal range by the same authors (4) (mean ±1 SD = 33.2 ±17.2 μg/24 hr). Two mothers (Nos. 4 and 5) had normal values, three had levels equal to 2.5 times the mean of Balikian et al. (4) (Nos. 8–10; in subjects 9 and 10 the production rates were calculated using the mean MCR of nine mothers), and one mother (No. 2) was almost 4 times the mean.

The small increases in plasma levels and blood production rates of aldosterone that we observed during late pregnancy contrast with the large elevations reported in the literature for production rate of aldosterone determined by “urinary” methods (13–15). When attempting to explain the difference in results, several points must be considered and discussed. Double isotope dilution techniques can give results which are erroneously high if the final extract of the compound studied is not purified. However, it cannot give results which are erroneously low, except if the method called for the subtraction of a blank from the value obtained for an unknown sample and if the blank happened to be overestimated. This did not appear to be the case in the present study since our water blank values were near zero. Modifications of aldosterone metabolism during pregnancy can explain the high values for aldosterone excretion as suggested by Jones et al. (13) and by Tait and Little (16). However, such metabolic changes will not influence the results of production rates which are obtained by the determination of the specific activity of a unique metabolite of aldosterone. As mentioned earlier, “urinary” methods for determination of aldosterone secretion rate are not valid for a two-compartment model with secretion and metabolism in each but injection of radioactive steroid in only one of them. Their results represent the sum of the maternal secretion and of an unknown fraction of the fetal secretion. It is doubtful, however, that the error inherent to the “urinary” methods could account for the large elevation previously reported. The most probable explanation for the apparent discrepancy between our results and those in the literature is the effect of posture on aldosterone secretion rate. The blood production in sitting position is 5 times greater than in supine position, while standing increases it 8-fold (4). Since our patients had been supine for at least 10 hr at the time of the study, it is understandable that their production was low when compared to the secretion of mothers who had been standing and sitting as well as supine during the 24 hr period of study. Our results should be taken into consideration when interpreting the effects of body posture on water and electrolyte metabolism during pregnancy (17).

**ACKNOWLEDGMENTS**

We wish to express our appreciation to Mrs. Baiba Ozolin for her expert technical assistance and to Miss Kathleen Scheller for her secretarial help.

This work was supported by U. S. Public Health Service Research Grant AM-00180, Traineeship T1-AM-5219, and Research Career Award 5K06 AM-21,855 (CJM).

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