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Acta Medica Okayama

Volume 39, *Issue* 4 1985 *Article* 2

AUGUST 1985

Catecholamines in amniotic fluid as indicators of intrapartum fetal stress.

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Abstract

Catecholamines were measured in the amniotic fluid and in the first voided newborn urine obtained from appropriate-for-date infants of term deliveries. Catecholamine values in the amniotic fluid and urine were nearly equal when expressed in terms of creatinine. Significant positive correlations were observed between the amniotic fluid and urine of norepinephrine and epinephrine. In normal cases (n = 32) that underwent uneventful vaginal delivery, the 95% confidence limits for norepinephrine and epinephrine in the amniotic fluid were 1.53 to 2.33 ng/ml and 0.16 to 0.30 ng/ml, respectively. In cases of moderate stress (n = 12), only norepinephrine showed significantly higher values than the normal cases, while in cases of severe stress (n = 12), norepinephrine became more significantly high, and epinephrine was found to be elevated significantly. A significant difference was noted in the incidence of fetal stress between the infants with more than and those with less than 2.30 ng/ml of norepinephrine, the upper limits of the normal 95% confidence limits. However, for epinephrine such a significant difference was not noted. It was concluded that amniotic fluid catecholamines are of fetal origin and reflect fetal sympathoadrenal activity directly, even during labor, and that their level may be a good indicator of fetal condition and stress.

KEYWORDS: amniotic fluid, fetal catecholamines, norepinephrine, epinephrine, intrapartum fetal stress

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*PMID: 4050534 [PubMed - indexed for MEDLINE]
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Acta Med. Okayama **39**, (4), 253-263 (1985)

CATECHOLAMINES IN AMNIOTIC FLUID AS INDICATORS OF INTRAPARTUM FETAL STRESS

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Received January 7, 1985

Abstract. Catecholamines were measured in the amniotic fluid and in the first voided newborn urine obtained from appropriate-for-date infants of term deliveries. Catecholamine values in the amniotic fluid and urine were nearly equal when expressed in terms of creatinine. Significant positive correlations were observed between the amniotic fluid and urine of norepinephrine and epinephrine. In normal cases (n=32) that underwent uneventful vaginal delivery, the 95 % confidence limits for norepinephrine and epinephrine in the amniotic fluid were 1.53 to 2.33 ng/ml and 0.16 to 0.30 ng/ml, respectively. In cases of moderate stress (n = 12), only norepinephrine showed significantly higher values than the normal cases, while in cases of severe stress (n = 12), norepinephrine became more significantly high, and epinephrine was found to be elevated significantly. A significant difference was noted in the incidence of fetal stress between the infants with more than and those with less than 2.30 ng/ml of norepinephrine, the upper limits of the normal 95 % confidence limits. However, for epinephrine such a significant difference was not noted. It was concluded that amniotic fluid catecholamines are of fetal origin and reflect fetal sympathoadrenal activity directly, even during labor, and that their level may be a good indicator of fetal condition and stress.

Key words : amniotic fluid, fetal catecholamines, norepinephrine, epinephrine, intrapartum fetal stress.

Delivery, even if it is normal, is a stress for the fetus. The fetus exhibits various physiological reactions in response to the stress of labor, and the analysis of fetal heart rates is now clinically performed by means of cardiotocography to detect fetal stress during labor.

It is widely recognized that the fetus secretes catecholamines in response to the stress of labor (1-7). In fact, catecholamine values in umbilical cord blood are high in cases of vaginal delivery, especially in cases of intrauterine asphyxia (2-6). Puolakka *et al.* (6) demonstrated that the determination of norepinephrine in umbilical cord blood could be used to monitor fetal stress during labor. If the dynamic state of the fetal sympathoadrenal system could be evaluated during labor, it would be a good indicator of the fetal condition and stress at the time of labor. However, the sampling of adequate fetal blood during labor is extremely limited. In contrast, amniotic fluid, which is thought to be one of the fetal com-

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partments, is easily obtained.

Therefore, the present study was designed to clarify the origin of amniotic fluid catecholamones and to assess amniotic fluid catecholamine concentrations under various fetal conditions and to determine whether these concentrations at delivery reflect fetal stress during labor. The possibility of the clinical application of the determination of catecholamines in amniotic fluid was discussed.

MATERIALS AND METHODS

Subjects. Amniotic fluid samples were obtained from 56 full-term vertex deliveries which ranged from 37 to 41 weeks of gestation. Gestational age was calculated from the last menstrual period, and in doubtful cases, it was confirmed by ultrasound evaluation. All the pregnant women had no medical complications during the antenatal period and delivered appropriate -for-date babies vaginally. In most cases, labor started spontaneously, but in a small number of cases, it was facilitated by administration of oxytocin, prostaglandin E_2 or prostaglandin $F_{2\alpha}$.

Amniotic fluid was collected vaginally at delivery. Amniotic fluid macroscopically contaminated by matermal blood was excluded. In some of the cases, first voided newborn urine was also collected using pediatric urine collection bags. Babies which did not void urine within 24 h of delivery were excluded from this study.

Immediately after collection, 0.1 ml of 6N hydrochloric acid and 10 mg of sodium metabisulfite were added to 5 ml each of the amniotic fluid and the first voided newborn urine. The samples were stored at -30℃ up to 4 weeks until assay.

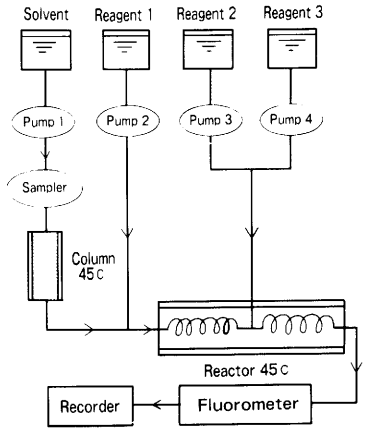
Classifications of the subjects. The subjects were classified into three main groups: normal group, moderately stressed group and severely stressed group according to intrapartum cardiotocographic recordings, meconium stained amniotic fluid and 1-minute Apgar scores. In the normal group ($n = 32$), the cardiotocographic recordings were essentially normal, no meconium stained amniotic fluid was found at delivery and 1-minute Apgar scores were above 8. The moderately stressed group ($n = 12$) showed abnormal cardiotocographic recordings which indicated fetal compromise but not fetal distress, moderately meconium stained amniotic fluid and/or 1-minute Apgar scores of 5 to 7. The severely stressed group ($n = 12$) consisted of cases that were diagnosed as fetal distress by cardiotocographic recordings according to the criteria of the Japan Society of Obstetrics and Gynecology (8) (namely, prolonged bradycardia (≤ 100 bpm), repetitive late decelerations over 15 min, severe variable deceleration and/or loss of baseline variability), and that showed strongly meconium stained amniotic fluid and/or 1-minute Apgar scores below 5.

Analytical procedure. The samples were first centrifuged through membrane cones (Amicon CENTRIFLO® type CF25) at 4℃. To each filtered sample, an equal volume of 2N hydrochloric acid was added. Hot acidic hydrolysis (100℃ for 20 min) was performed in order to measure the total compounds (free and conjugated forms).

After hydrolysis, 200 mg of ethylenediaminetetraacetic acid (EDTA) was added, and the pH was adjusted to 8.5 with sodium carbonate-bicarbonate buffer while stirring continuously. The catecholamines were then adsorbed on 200 mg of aluminum oxide (Woelm Pharma Alumina Woelm® N, Akt 1) packed in a glass column (7 mm i.d. × 100 mm). After adsorption, the column was rinsed with distilled water until the effluent became neutral, and the catecholamines were eluted with 2 ml of 0.2N acetic acid added in 2 aliquots. For the urine, 50 μl of the eluate was applied to the catecholamine assay. For the amniotic fluid, the eluate was lyophilized,

and the residue was dissolved in 100 μl of 0.2N acetic acid. Then, 50 μl of the solution was used for analysis.

Separation of each catecholamine fraction was carried out by means of high performance liquid chromatography (HPLC) using a cation exchange column (Hitachi gel # 3011-C), and the determination of each catecholamine was performed by the automated trihydroxyindole method (9). The conditions, reagents and functional diagram of the HPLC and trihydroxyindole method are shown in Fig. 1.



Column	: 2.6mm×250mm
Gel	: Hitachi gel 3011-C
Column Temp.	: 45℃
Reactor Temp.	: 45℃
Solvent	: 0.1M KH_2PO_4
	0.05% v/v H_3PO_4
Reagent 1	: 0.1M KH_2PO_4
	0.2M K_2HPO_4
	0.0075% v/v $K_3Fe(CN)_6$
Reagent 2	: 0.1% v/v Ascorbic Acid
Reagent 3	: 5N NaOH
Flow Rate	: Solvent 0.6 ml/min
	Reagent 0.2 ml/min
Pressure	: 35 kg/cm²
Fluorometer	: Ex. Wavelength 410 nm
	Slit Width 20 nm
	Em. Wavelength 510 nm
	Slit Width 20 nm

Fig. 1. The conditions, reagents and functional diagram of the high performance liquid chromatographic system employing the automated trihydroxyindole method for catecholamine assay.

The mean recovery of dopamine, norepinephrine and epinephrine in this assay was 67.7 ± 5.6 %, 59.8 ± 3.5 % and 54.7 ± 3.4 % (mean ± standard deviation), respectively, in 9 determinations. The assay sensitivity was 2,500 pg for dopamine, 30 pg for norepinephrine and 35 pg for epinephrine.

Creatinine in the amniotic fluid and the first voided newborn urine was also measured with a Technicon Auto Analyzer® in order to express the catecholamine values as per mg of creatinine.

All catecholamine values in this study were given as total compounds (free and conjugated catecholamines) and expressed as mean ± standard error. Statistical analyses were performed by one-way analysis of variance (ANOVA), chi-square analysis and linear regression analysis.

RESULTS

Correlations between catecholamine values in the amniotic fluid and the first voided newborn urine. Three catecholamines, dopamine, norepinephrine and epinephrine, were detected in both the amniotic fluid and the first voided newborn urine. In the normal group, the values of dopamine, norepinephrine and epinephrine were 1,239.11 ± 176.08, 137.30 ± 20.58 and 14.52 ± 2.23 ng/mg of creatinine, respectively. In

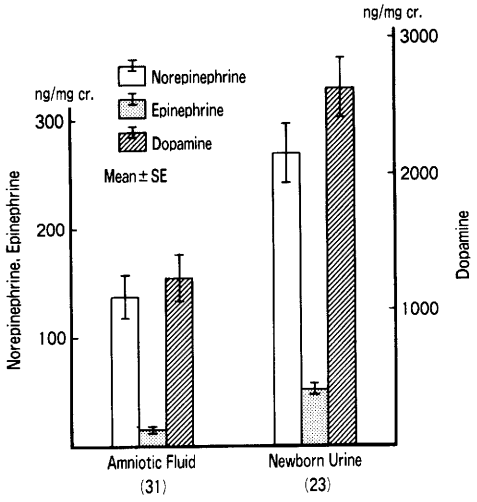


Fig. 2. The mean values of catecholamines in the amniotic fluid and in the first voided newborn urine from normal cases delivered vaginally at 37-41 weeks of gestation. All values are expressed as ng per mg of creatinine. The numbers of subjects are shown in parentheses.

the first voided newborn urine, these values were $2,634.84 \pm 220.74$, 269.42 ± 26.75 and 51.17 ± 4.60 ng/mg of creatinine, respectively (Fig. 2). The mean values of each catecholamine fraction in the first voided newborn urine, when expressed as ng per mg of creatinine, were about 2 to 3.5-fold higher than those in the amniotic fluid. However, the composition ratio (dopamine : norepinephrine : epinephrine) was nearly the same in the amniotic fluid as in the first voided newborn urine.

There were significant positive correlations between catecholamine concentrations in the amniotic fluid and the first voided newborn urine. The regression line for norepinephrine was $Y = 0.0296X - 0.4375$ ($r = 0.82$, $n = 21$, $p < 0.001$), and for epinephrine, $Y = 0.0114X + 0.0398$ ($r = 0.58$, $n = 21$, $p < 0.01$), where Y = concentration in the amniotic fluid (ng/ml) and X = concentration in the first voided newborn urine (ng/ml).

Norepinephrine and epinephrine values in the amniotic fluid and the first voided newborn urine in the normal group. In the normal group, catecholamine values in the amniotic fluid, when expressed as ng per ml, were 1.93 ± 0.20 ng/ml for norepinephrine

TABLE 1. THE MEAN VALUES AND THE 95% CONFIDENCE LIMITS OF NOREPINEPHRINE AND EPINEPHRINE IN THE AMNIOTIC FLUID FROM NORMAL CASES DELIVERED VAGINALLY AT 37-41 WEEKS OF GESTATION

	Mean ± SE	95 % Confidence limits
Norepinephrine (32)	1.93 ± 0.20	1.53 ~ 2.33
Epinephrine (32)	0.23 ± 0.03	0.16 ~ 0.30

All values are expressed as ng per ml with the numbers of subjects in parentheses.

and 0.23 ± 0.03 ng/ml for epinephrine, and the 95 % confidence limits for norepinephrine and epinephrine in the amniotic fluid were 1.53 to 2.33 ng/ml and 0.16 to 0.30 ng/ml, respectively (Table 1).

In the first voided newborn urine, the catecholamine values were, norepinephrine, 145.10 ± 19.00 ng/ml, and epinephrine, 30.10 ± 3.28 ng/*ml*. These urinary catecholamine values were about one hundred times higher than those in the amniotic fluid.

Norepinephrine values in the amniotic fluid and fetal stress. Individual values of amniotic fluid norepinephrine in the normal cases and the stressed (moderate and severe) cases are given in Fig. 3. A norepinephrine concentration of 2.33 ng/ml

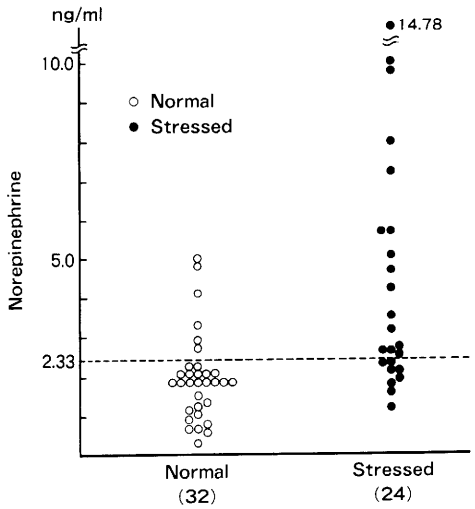


Fig. 3. The amniotic fluid norepinephrine values in normal cases (open circles) and stressed cases (closed circles). The broken horizontal line represents the upper limit of the normal 95 % confidence limits.

TABLE 2. THE INCIDENCE OF FETAL STRESS WITH AMNIOTIC FLUID CATECHOLAMINE VALUES ABOVE OR BELOW THE UPPER LIMIT OF THE NORMAL 95 % CONFIDENCE LIMITS

Amniotic fluid catecholamines	n	Stressed case	
		No.	%
Norepinephrine			
≥ 2.33 ng/ml	22	16	72.7 *
< 2.33 ng/ml	34	8	23.5 *
Epinephrine			
≥ 0.30 ng/ml	21	13	61.9
< 0.30 ng/ml	35	11	31.4

* $p < 0.001$

represents the upper limit of the 95 % confidence limits for the concentrations of amniotic fluid norepinephrine in the normal cases.

All the cases were divided into two groups according to whether the norepinephrine value was above or below this limit (Table 2). Twenty-two of 56 cases had norepinephrine values in excess of 2.33 ng/ml, and sixteen of the 22 cases (72.7 %) were stressed. The remaining 34 cases had values of norepinephrine below 2.33 ng/ml. Only eight of these 34 cases (23.5 %) were stressed. There was a significant difference in the incidence of fetal stress between the two groups ($p < 0.001$) (Table 2).

Epinephrine values in the amniotic fluid and fetal stress. The upper limit of the 95 % confidence limits for the values of amniotic fluid epinephrine in the normal cases was 0.30 ng/ml, and grouping of all the cases was performed according to this limit.

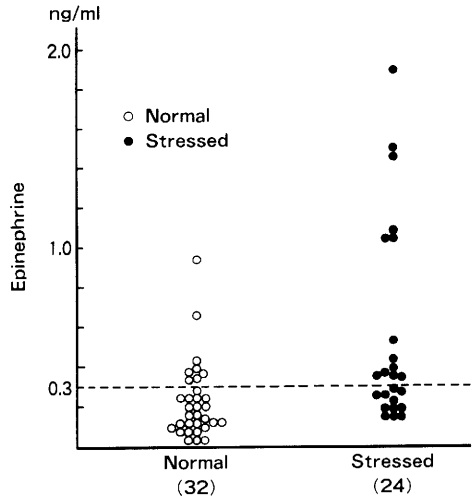


Fig. 4. The amniotic fluid epinephrine values in normal cases (open circles) and stressed cases (closed circles). The broken horizontal line represents the upper limit of the normal 95 % confidence limits.

As shown in Fig. 4 and Table 2, 21 of 56 cases had epinephrine values above this limit, and 35 had values below this limit. In the first group, thirteen cases were stressed (61.9 %). In the second group, eleven cases (31.4 %) were stressed. No significant difference was noted in the incidence of fetal stress between the two groups. However, in cases of severe stress, a significant difference was observed between the two groups (52.9 % versus 11.1 %, $p < 0.01$).

Severity of fetal stress and the values of catecholamines in the amniotic fluid. As shown in Fig. 5, the mean values of norepinephrine in the amniotic fluid were 1.93 ± 0.20 ng/ml in the normal group, 2.93 ± 0.38 ng/ml in the moderately stressed group

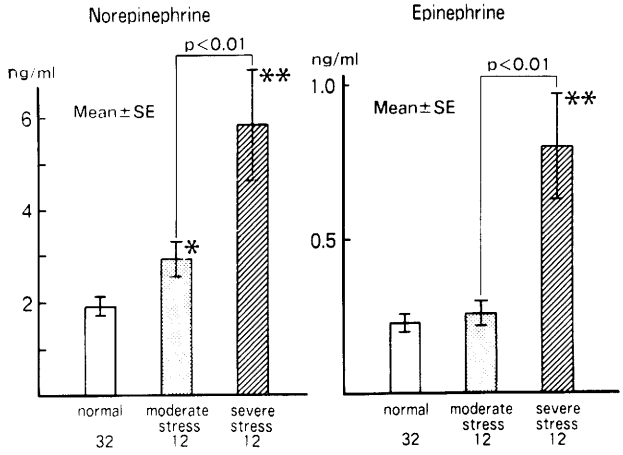


Fig. 5. The relationships between the values of amniotic fluid catecholamines and the severity of fetal stress. The numbers of subjects are shown in parentheses. Significant difference from the normal value by one-way ANOVA : * $p < 0.05$, ** $p < 0.01$.

and 5.84 ± 1.20 ng/ml in the severely stressed group. The mean values of amniotic fluid norepinephrine became higher with an increase in severity. There were significant differences between each group (normal versus moderate : $p < 0.05$, moderate versus severe : $p < 0.01$, normal versus severe : $p < 0.01$). The mean values of amniotic fluid epinephrine were 0.23 ± 0.03 ng/ml in the normal group, 0.26 ± 0.04 ng/ml in the moderately stressed group and 0.80 ± 0.17 ng/ml in the severely stressed group. Significant elevation of epinephrine values was noted only in the severely stressed group as compared to the normal group ($p < 0.01$) and the moderately stressed group ($p < 0.01$).

DISCUSSION

In 1970, Zuspan and Abott (10) first identified catecholamines in human amniotic fluid, and they speculated that catecholamines in amniotic fluid might be of fetal origin. Since that time, there have been some indirect observations which support this speculation. Dalmaz *et al.* (11) have demonstrated a pattern of catecholamine excretion in term newborn urine identical to that observed in amniotic fluid. Muskiet *et al.* (12) reported that 3-methoxy-4-hydroxyphenylglycol (MHPG), 3-methoxy-4-hydroxyphenylacetic acid (HVA) and 3-methoxy-4-hydroxyphenylmandelic acid (VMA), when expressed in terms of creatinine, had similar values in amniotic fluid and newborn urine. Multiple studies (13-15) have suggested that catecholamines do not cross the placenta in large quantities because of the abundance of catecholamine metabolizing enzymes, *e.g.*, monoamine oxidase and catechol-O-methyltransferase, in the human placenta. However, there are few observations that prove the origin of amniotic fluid catecholamines directly.

The present results obtained from the analysis of the relationships between the catecholamine values in the amniotic fluid and the first voided newborn urine strongly suggest that catecholamines in the amniotic fluid originate from the fetal urine and reflect the activity of the fetal sympathoadrenal system directly. It may be possible to analyze the dynamic state of the fetal sympathoadrenal system by measuring catecholamines in amniotic fluid.

Various stimuli are known to evoke a fetal catecholamine response in animal models (16-18). Comline *et al.* (16) demonstrated that hypoxia is a very potent stimulus of catecholamine secretion from the adrenal medulla in the fetal lamb. In the human, many previous studies (1-7) have demonstrated a significant sympathoadrenal response to labor stress in the fetus at term. Higher levels of catecholamines in the umbilical artery have been observed after normal vaginal delivery than elective abdominal delivery (3, 6), and increased catecholamine values have been found in fetal scalp blood during the second stage of labor (7). Furthermore, catecholamines, especially norepinephrine, in the umbilical artery were significantly elevated in cases of complicated deliveries, such as intrapartum fetal asphyxia and breech delivery (2-6). Puolakka *et al.* (6) measured umbilical cord blood norepinephrine values in various deliveries and concluded that determinations of plasma norepinephrine in the umbilical artery can be used to monitor fetal stress during labor.

The values of norepinephrine and epinephrine in the amniotic fluid in the present study were higher than those reported by Phillippe and Ryan (19), which were obtained before the onset of labor and analyzed as free catecholamines by radioenzymatic assay. Although our catecholamine values were expressed as total componuds, free catecholamines constitute approximately 80 % of the total catecholamines in the newborn urine analyzed by the trihydroxyindole method (11, 20) ; hence, the calculated free norepinephrine values of our normal group are much higher than those of Phillippe and Ryan. This difference in norepinephrine values in the amniotic fluid before and after labor can be interpreted as evidence of increased fetal norepinephrine release into the amniotic fluid during labor, and also indicates that normal vaginal delivery is a stress for the fetus. Artal *et al.* (21) likewise observed an increase in free metanephrine, a metabolite of catecholamines, in the amniotic fluid during labor.

It was assumed that the much higher catecholamine values are the result of further activation of the fetal sympathoadrenal system as a defense reaction aganist the strong stress. Therefore, the incidence of fetal stress as judged by cardiotocographic recordings, meconium stained amniotic fluid and Apgar scores was studied with regard to the upper limit of the normal 95 % confidence limits. As a result, a significant difference was noted in the incidence of fetal stress for norepinephrine. Namely, the incidence of fetal stress was 72.7 % in the cases with norepinephrine levels above 2.33 ng/ml. This result indicates that it is possible to detect fetal stress by measuring norepinephrine in amniotic fluid.

Zuspan *et al.* (22) reported an increase in amniotic fluid norepinephrine and epinephrine caused by fetal stress following methadone treatment of pregnant women. Furthermore, Lagercrantz *et al.* (23) demonstrated that MHPG and, particulary, the MHPG/VMA ratio in the amniotic fluid before labor were significantly higher in intrauterine growth retarded cases than in uncomplicated cases, and indicated the possibility that the analysis of catecholamine metabolites in amniotic fluid might be useful for the assessment of intrauterine distress. In addition, significant elevations of norepinephrine, epinephrine and 3, 4-dihydroxyphenylacetic acid (DOPAC) values were observed in the amniotic fluid of growth retarded cases and smokers, suggesting an increase in fetal adrenergic activity in response to chronic intrauterine stress (24, 25). From the present investigation, it was confirmed that norepinephrine in amniotic fluid is also useful for the evaluation of acute stress even at the time of labor.

The false positive rate in evaluating fetal stress by amniotic fluid norepinephrine values in this study was 27.3 percent. It can be speculated that fetal norepinephrine is a more sensitive parameter of fetal stress than other clinical parameters such as cardiotocographic recordings, meconium stained amniotic fluid and Apgar scores. Further studies into this problem are necessary. In contrast, the false negative rate was somewhat high (23.5 %). This high false negative rate may be partly attributed to the time lag between the activation of fetal sympathoadrenal system by stress and fetal voiding.

Although the stressed cases in this study included all cases from moderately meconium stained cases to severely stressed cases, it may be inappropriate to treat them as the same group clinically. When the stressed cases were divided into the moderately stressed group and the severely stressed group, the mean values of amniotic fluid norepinephrine increased significantly in accordance with the severity of fetal stress, showing graded norepinephrine release in response to stress. Epinephrine, however, showed a significant increase only in the severely stressed group.

In term fetal sheep, the secretion of catecholamines correlates well with the severity of hypoxia (18). According to Comline *et al.* (16), the release of catecholamines from the fetal adrenal medulla is caused mainly by the decrease in fetal blood PO_2; norepinephrine is secreted first, then when PO_2 decreases to 8 mmHg, epinephrine is also secreted, and below 4 mmHg the release of both amines becomes maximal. In the human fetus, norepinephrine values in the umbilical artery have been found to be higher than epinephrine values (3-5) and elevated in proportion to the degree of stress (2). Padbury *et al.* (5) demonstrated significant positive correlations between umbilical arterial norepinephrine and pH and PCO_2, and between umbilical arterial epinephrine and pH, observing significantly elevated epinephrine in fetuses which showed moderate to severe variable decelerations or late decelerations in cardiotocographic recordings. From these results, they speculated that there may be a critical threshold for stimulation of epinephrine release

as has been demonstrated in fetal sheep (18).

The present study has confirmed that, as to the secretion of fetal catecholamines during fetal stress, norepinephrine is the predominant amine and its secretion increases in proportion to the degree of stress. However, when the stress reaches an extreme state at which the fetal heart rate tracings exhibit the patterns of fetal distress, i.e., repetitive severe variable decelerations, repetitive late decelerations, marked bradycardia and/or loss of variability, epinephrine is released in large quantities. These results are in agreement with a previous study (5) of umbilical arterial catecholamines. It seems likely that the degree of fetal stress may be assessed from the fractional value of each catecholamine in amniotic fluid.

In conclusion, the authors have demonstrated that catecholamines in amniotic fluid are of fetal origin, and that their level is a good biochemical parameter to monitor fetal stress even during labor. This fetal monitoring using amniotic fluid catecholamine determinations could further aid in predicting fetuses suffering chronic intrauterine stress during the antenatal period. In the near future, determinations of catecholamines in amniotic fluid may be utilized to evaluate fetal stress and understand fetal functions more precisely in conjunction with biophysical assessments.

Acknowledgement. The authors wish to thank Prof. Kaoru Sekiba for his valuable suggestions and kind guidance in this study. This study was supported in part by a research grant from the Ministry of Health and Welfare of Japan.

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