The Incidence of Meconium-Aspiration in Hawaii

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Meconium in the amniotic fluid was found in 2,633 obstetrical patients and meconium-aspiration occurred in 77 cases out of 14,527 deliveries. Although the incidence of meconium in the amniotic fluid increased significantly at 39 weeks, a corresponding significant increase in meconium-aspiration did not occur until 41 weeks gestation. All deaths associated with meconium, as well as 84% of the cases of severe meconium-aspiration syndrome, occurred in infants born of patients with oligohydramnios and a gestational age of 41 weeks or greater.

Introduction

The incidence of meconium-stained amniotic fluid appears to increase with gestational age[1,2] but the significance of meconium has been controversial as a risk-factor for adverse perinatal outcome. Meconium does increase the potential for perinatal morbidity and mortality when it is associated with the meconium-aspiration syndrome. The majority of cases of meconium-aspiration syndrome has occurred in association with fetal distress[3-5] but meconium-aspiration has been noted in the presence of a normal fetal heart-rate pattern[6] and prior to the onset of active labor[7]. The purpose of our study was to document the incidence of meconium present in the amniotic fluid, and to see if a correlation existed with the meconium-aspiration syndrome and advancing gestational age.

Materials and Methods

A detailed review of 14,527 deliveries during the past 2 consecutive years identified 2,633 cases of meconium in the amniotic fluid and 77 cases of meconium-aspiration syndrome. All pregnancy and fetal outcomes were obtained from a careful review of the prenatal, labor and delivery, and neonatal records. Gestational age was determined from a review of menstrual history, ultrasound examination and antenatal records. The gestational ages of all 77 mothers whose infants had meconium-aspiration syndrome were documented by early ultrasound.

Meconium was graded by the physician in attendance as thick, moderate, or thin. The presence of meconium in amniotic fluid obtained preterm was confirmed by spectrophotometric analysis. In the infant, the diagnosis of meconium-aspiration required finding meconium in the trachea, clinical signs of respiratory distress, and a chest x-ray consistent with meconium-aspiration. Oligohydramnios was diagnosed by ultrasound or by the clinical absence of fluid in the mother documented during labor and delivery.

Meconium-aspiration was considered to be severe when infants had to be placed on a respirator for ventilatory support. All infants with the syndrome were subjected to aggressive airway management. This included pharyngeal functioning with a DeLee catheter at delivery of the head, followed by visualization of the vocal cords and suctioning of the trachea under direct vision by a member of the pediatric house staff. Obstetrical patients who had meconium in the amniotic fluid and whose infants developed the meconium-aspiration syndrome were analyzed in relation to gestational age. Statistical evaluation was done by chi square analysis; the probability was considered to be significant at $P=<0.05$.

Results

The presence of meconium was documented in 2,633 cases (18%) out of 14,527 deliveries between 28 and 45 weeks of gestation. The syndrome itself was diagnosed in 77 deliveries (0.05%). Between 28 and 36 weeks' gestation, meconium was found in 153 cases (10.7%) out of 1,426 deliveries. Between 37 and 41 weeks, meconium was found in 2,305 cases (18.5%) out of 12,487 deliveries. After 41 weeks, meconium was found in 175 cases (28.5%) out of 614 deliveries. The incidence of parturient patients who had meconium in the amniotic fluid, and whose infants went on to have the meconium-aspiration syndrome, remained relatively constant with increasing gestational age from 28 to 36 weeks (Table 1). However, at 39 weeks the incidence increased considerably, followed by a significant increase in the meconium-aspiration syndrome in the infant at 41 weeks (Table 2). A significant increase in the meconium-aspiration syndrome occurred in cases that demonstrated meconium in the amniotic fluid pre-delivery at 41 weeks (Table 3).

The aspiration of meconium by the infant was diagnosed in 7 patients who delivered prior to 38 weeks' gestation. Four of these demonstrated thin meconium and 3 had moderately thick meconium. Very thick meconium was not found in any infant with the aspiration syndrome whose mother delivered prior to the 38-week period. On the other hand, at 39 weeks and beyond, 91% of the infants with the syndrome presented with very thick meconium.

Oligohydramnios was characteristic of 29 out of 31 mothers (94%) whose infants demonstrated the meconium-aspiration syndrome, mothers whose gestational ages were 41 weeks or beyond.

There was a 63% rate of fetal distress and a 57% rate of

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delivery by C-section in the cohort of women whose infants were diagnosed as having the syndrome. However, of the women who had oligohydramnios at 41 weeks or beyond, 90% exhibited fetal distress and 83% of them had to have C-sections.

Term infants with the syndrome spent a mean of 4 days in the neonatal intensive care unit and were hospitalized for an average of 11 days in all. Severe aspiration of meconium was diagnosed in 84% of the infants delivered at 41 weeks' gestation and beyond. The 3 infants who died of meconium-aspiration were delivered by cesarean section, the indication being fetal distress; all 3 were found to have aspirated thick meconium. Two of these infants were delivered after 41 weeks of gestation, and the third was delivered after 42 weeks.

TABLE 1: Gestational Age, Meconium Staining of Amniotic Fluid and Meconium-Aspiration Syndrome

Gestational Age	Deliveries	Meconium Staining	Percentage Deliveries	Meconium Aspiration	Percentage Deliveries
28	60	11	18.3%	1	1.7%
29	37	3	8.1%	0	—
30	74	10	13.5%	0	—
31	69	8	11.6%	0	—
32	119	15	12.6%	1	0.8%
33	138	12	8.7%	0	—
34	191	20	10.5%	3	1.6%
36	474	44	9.3%	1	0.2%

TABLE 2: Gestational Age, Meconium Staining of Amniotic Fluid and Meconium-Aspiration Syndrome

Gestational Age	Deliveries	Meconium Staining	Percentage Deliveries	Meconium Aspiration	Percentage Deliveries
37	963	115	11.9%	1	0.1%
38	2,177	281	12.9%	7	0.3%
39	3,493	621	17.7%	9	0.3%
40	4,165	874	21.0%	22	0.5%
41	1,689	414	24.5%	21	1.2%*
42	518	151	29.2%	10	1.90%
43	84	20	23.8%	0	—

**P=<0.005 between the current and previous weeks of pregnancy.

TABLE 3: Gestational Age and Meconium-Aspiration Syndrome in Patients with Meconium at Birth

Gestational Percentage	Meconium at Birth	Meconium Aspiration	Percentage
37	60	11	18.3%
38	37	3	8.1%
39	74	10	13.5%
40	69	8	11.6%
41	119	15	12.6%
42	138	12	8.7%
43	191	20	10.5%

**P=<0.025 between the current and previous weeks of pregnancy.

Comment

In this study meconium was found to be present in 10.7% of the infants delivered preterm. Matthews and Warshaw[2] did not find any meconium in patients at less than 34 weeks of gestation, but Parida[8] found meconium in 3.7% of such cases. Ostrea and Naqvi[9] found a 2.6% incidence in their preterm patients. Green and Paul[10] found a 6% incidence between 29 and 36 weeks of gestation, and in 8% of their patients prior to 29 weeks' gestation.

In our study, spectrophotometric analysis used to document the presence of meconium in the amniotic fluid could account for the higher percentage of preterm patients positive for the presence of meconium. Although meconium was found in 10.7% of preterm patients, the incidence of meconium-aspiration in the infants delivered remained at a low of 0.5%. A significant increase in the presence of meconium was documented at 39 weeks' gestation. This increase at 39 weeks also has been reported by Eden[1] and Green[10] and represents a normal physiologic indicator of fetal maturation[11] or compression of the cord in the mature fetus[12].

The impression that the presence of meconium alone, in the absence of any other risk factors, is a normal result of fetal maturation can be supported by the uneventful outcome of the majority of fetuses delivered despite the presence of meconium as reported in all studies[10].

The significant increase in meconium at 39 weeks documented in our study was not accompanied by an increase in the meconium-aspiration syndrome until 41 weeks of gestation had been reached. This appears to confirm the finding that meconium alone is not a good predicter of adverse fetal outcome[13]; other factors besides the presence of meconium must be taken into account.

When fetal asphyxia is associated with meconium, it appears that the potential for perinatal morbidity and mortality is increased[14,15]. Miller has suggested that fetal asphyxia with the presence of meconium can increase the potential for meconium-aspiration and poor neonatal outcome[16]. Grausz and Heimler reported that 5% of infants who died of unexpected asphyxia did so prior to 40 weeks' gestation, compared to 32.5% at 40 to 41 weeks and 37.5% after 41 weeks[17]. A similar gestational age distribution was found in their neurologically affected group of infants which led to the conclusion that pregnancies beyond 40 weeks require meticulous assessment of fetal well-being both before and during labor because this is the most frequently observed time for unexpected asphyxia[17].

A decrease in amniotic fluid appears to be another factor in the meconium-aspiration syndrome. Amniotic fluid volume remains relatively constant until the 37th week of gestation; it declines gradually until the 40th week. After 40 weeks, amniotic fluid diminishes rapidly in a certain percentage of patients; the lowest amniotic fluid volumes are found at 41 weeks' gestation or later[18]. Of greater importance, is Clement's report that amniotic fluid volume could decrease significantly in less than 24 hours in post-dated pregnancies[19].

Based on these studies, it appears that the fetus beyond 40 weeks with meconium in the amniotic fluid and oligohydramnios in the mother is at very high risk for developing unexpected fetal asphyxia. The decrease in volume can lead to the

bone marrow assay.

Enalapril Maleate: There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times* the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times* the maximum daily dose for humans) and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.

Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy; Pregnancy Categories C (first trimester) *and D* (second and third trimesters). See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*

Nursing Mothers: Enalapril and enalaprilat are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent), and diarrhea (2.1 percent).

Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: *Body As A Whole:* Syncope, chest pain, abdominal pain; *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia; *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth; *Nervous/Psychiatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo; *Skin:* Pruritus, rash; *Other:* Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, *Cough.*

Clinical Laboratory Test Findings; Serum Electrolytes: See PRECAUTIONS.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, and Calcium: See PRECAUTIONS.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.

Enalapril Maleate—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Body As A Whole:* Anaphylactoid reactions (see PRECAUTIONS, *Hemodialysis Patients*); *Cardiovascular:* Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; hypotension; angina pectoris; *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, glossitis, stomatitis, dry mouth; *Hematologic:* Rare cases of neutropenia, thrombocytopenia and bone marrow depression. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril has not been established. *Nervous System/Psychiatric:* Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia); *Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, gynecomastia; *Respiratory:* Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection; *Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pemphigus, alopecia, flushing, photosensitivity; *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*

Hydrochlorothiazide—Body as a Whole: Weakness; *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia; *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions; *Musculoskeletal:* Muscle spasm; *Nervous System/Psychiatric:* Restlessness; *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS); *Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; *Special Senses:* Transient blurred vision, xanthopsia.

* Based on patient weight of 50 kg.

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meconium being thicker, which would make it more difficult for the trachea to be cleared at the time of delivery. Decreasing amniotic fluid volume also can also lead to compression of the umbilical cord causing a further expression of meconium into the amniotic fluid. This would increase the likelihood of the in utero infant aspirating the meconium[20].

In our study, the incidence of aspiration of meconium remained at a relatively low level between 28 and 40 weeks of gestation. The incidence increased after 40 weeks' gestation and rose significantly at 41 weeks. All fetal deaths and 84% of the severe cases of meconium-aspiration in this study occurred at 41 weeks and beyond. In some centers, there is a trend to begin the induction of labor or surveillance of the fetus at the end of 41, and even 40, completed weeks because of a small number of unexplained stillbirths[21]. It appears that delivery prior to 41 weeks in a patient with oligohydramnios and the presence of meconium would significantly decrease the incidence of the most serious complications associated with the meconium-aspiration syndrome.

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