The Effect of Amniotic Fluid Aspiration on Pulmonary Function in the Adult and Newborn Rabbit

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Summary

Aspiration of uncontaminated human amniotic fluid was investigated in adult and newborn rabbits and compared with three other experimental groups: 10% meconium solution, saline, and sham-injected controls. Fluids were injected into the trachea of adult animals (4 or 6 ml/kg body weight), newborn vaginally-delivered animals (a mean volume of 8 ml/kg), and cesarean-delivered animals before their first breath (a mean volume of 11 ml/kg).

In adult animals aspirating amniotic fluid or saline, arterial PO_2 measured over a 24-h period showed a mean difference between groups of <5% for both 4 and 6 ml/kg. Meconium aspiration produced a greater depression in PO_2 than amniotic fluid aspiration (a mean difference of 16 and 31% for 4 and 6 ml/kg, respectively) and animals aspirating meconium showed a deteriorating trend over 24 h, whereas animals aspirating amniotic fluid improved. One of eight adult animals aspirating amniotic fluid died *versus* four of five aspirating meconium. All five animals aspirating saline 6 ml/kg survived. Lung weight and resting volume of adult animals aspirating amniotic fluid were not significantly different from animals aspirating saline or nothing. Lung pressure volume curves from adult animals aspirating amniotic fluid were nearly identical to controls. Histology showed significantly greater atelectasis in adult animals that received 6 ml/kg amniotic fluid than controls, but this was not different from saline. There was no association between the number of cells in amniotic fluid and arterial PO_2 after aspiration or any other aspect of pulmonary function measured.

Newborn rabbits aspirating human amniotic fluid were not significantly different from those aspirating saline and non-aspirating controls with respect to mortality, respiratory rates, lung weights, static deflation curves, chest radiographs, or lung histology. This was in marked contrast to the effects of aspiration of an equal volume of 10% meconium solution, which produced a mortality of 100%. We conclude that aspiration of human amniotic fluid is unlikely to be associated with specific lung disease.

The significance of meconium aspiration in neonatal respiratory disease is well established, but there remains some controversy as to the consequences of aspiration of uncontaminated amniotic fluid. Schaffer and others described a syndrome in which respiratory distress in premature and term infants was caused by the aspiration of amniotic fluid and its cellular contents, usually following asphyxia (2, 19, 23). This conclusion was supported by postmortem findings of squamous cells in the airways of infants dying of respiratory failure, although squamous

debris has also been demonstrated in the lungs of infants dying of non-respiratory causes (2). Also, there does not appear to be a consensus on the severity of respiratory compromise, if any, that results from aspiration of amniotic fluid. Some authors suggest that it can cause serious and even fatal pulmonary disease (23) whereas others contend that it causes only mild or moderate respiratory distress (26), or that its role in respiratory disease "remains to be demonstrated" (2, 6). Pathophysiologic mechanisms proposed in addition to airway obstruction by squamous cells include added lung water (15) and surfactant washout (24). Studies of this syndrome in laboratory animals have displayed variable responses to amniotic fluid aspiration (15, 16, 24, 29), and have usually utilized species-specific amniotic fluid, which may differ substantially from that of the human fetus (21). We wished to determine if human amniotic fluid was unique in its harmful effects on pulmonary function. This report evaluates the effect of aspiration of human amniotic fluid on the adult and newborn rabbit.

MATERIALS AND METHODS

Aspiration was induced in adult New Zealand white rabbits as well as vaginally and cesarean delivered newborn pups in a manner patterned after previous studies of meconium aspiration (8, 9). Human amniotic fluid was compared with three other experimental groups: 10% human meconium solution, saline, and sham-injected controls. Meconium provided a "positive" control so that any respiratory compromise caused by aspiration of amniotic fluid could be compared with a well-characterized aspiration syndrome. Saline provided a "negative control" so that effects of amniotic fluid aspiration could be compared with a simple drowning response.

Adult rabbits. Human amniotic fluid was acquired from samples obtained at diagnostic amniocentesis and utilized within 24 h. Cell counts were performed on all samples, and the amniotic fluid and meconium samples were cultured to confirm sterility. Aspiration fluids were administered through a teflon catheter introduced into the trachea by percutaneous puncture and threaded to a point just above the carina. Arterial blood samples were obtained from an indwelling arterial catheter placed percutaneously in the animal's ear. PO_2 , PCO_2 and pH were determined at 10, 30, 60, 90, and 120 min, and 6 and 24 h after aspiration.

Pressure-volume curves were obtained with the thorax closed (5, 22) after spontaneous death or sacrifice at 24 h. The trachea was then clamped at 0 cm H_2O and lung displacement in water was determined. The residual lung volume was calculated by subtracting the wet lung weight, assuming that the lung tissue specific gravity was approximately 1.0 g/ml. Representative sam-

ples were taken from each set of lungs, fixed in formalin, and stained with hematoxylin and eosin for study by light microscopy by one of us (L.D.M.) who had no prior knowledge of the experimental group to which each specimen belonged.

Vaginally-delivered pups. Seven does were allowed to deliver vaginally on days 31–33 of gestation (31 days is term). Four hundred-fifty μ l (mean 8 ml/kg) of each fluid was injected through a teflon catheter (22 gauge Angiocath) introduced into the trachea by percutaneous puncture. The presence of the catheter in the trachea was confirmed by the aspiration of air before injection. Injection occurred at times after birth ranging from 3 min–4 h (mean, 2.1 h).

Cesarean-delivered pups. Twelve does of known gestational age were delivered by cesarean section after spinal anesthesia (23) on day 30–31 of gestation. Arterial blood gases were obtained from the does to document appropriate maternal ventilation before and after cesarean delivery. After delivery of the fetal head through a small incision in the uterus, 450 μ l of each fluid (a mean volume of 11 ml/kg body weight) was injected in the manner described above. The time from skin incision to the delivery of the last pup ranged from 3–7 min. Technetium 99 sulfur colloid was placed in each fluid sample, and the pups were discarded if a gamma scan did not demonstrate the fluid in their lungs. Radiographs were performed on the cesarean delivered pups at less than 2 h age and repeated at 24–32 h. The radiographs were interpreted by one of us (M.C.) without knowledge of experimental grouping.

All pups were placed in an incubator at 36–37°C and oxygen was administered for 30–60 min. Respiratory rates were recorded every 8 h. The animals were fed 5–6 ml of 24 cal/oz infant formula by gavage drip twice during the 48-h period. Survivors were sacrificed at 48 h and quasi-static lung deflation curves were performed after degassing the lungs with 100% oxygen (4, 7, 17, 27). The system was checked for leaks before each use and a peak distending pressure of 25 cmH₂O was maintained for 10 min. Body weight, lung weight, and lung histology were also obtained at 48 h. The groups aspirating amniotic fluid were compared with the other groups using analysis of variance with group-specific differences being determined by using the “least significant difference” method (25).

RESULTS

Adult rabbits. Arterial blood gases (Figs. 1 and 2) were analyzed by three factor analysis of variance. Amniotic fluid aspiration

produced a slightly greater depression in PO_2 than saline (a mean difference of $5 \pm 2\%$, $P = 0.0076$ and $5 \pm 2\%$, $P = 0.016$ for 4 ml/kg and 6 ml/kg, respectively). Meconium caused a much greater depression in PO_2 than amniotic fluid (a mean difference of $16 \pm 2\%$, $P < 0.0001$ and $31 \pm 3\%$, $P < 0.0001$). Animals receiving amniotic fluid or saline improved after the initial depression, whereas the meconium aspiration group either stabilized at a depressed level or deteriorated with time. Arterial pH and PCO_2 after aspiration of amniotic fluid or saline were not significantly different from controls.

One of eight adult animals died after aspirating 6 ml/kg amniotic fluid whereas an equal volume of 10% meconium solution resulted in death in four of five animals (Table 1). The lung weights of animals aspirating amniotic fluid were not significantly different from those of animals aspirating saline or nothing (Table 1). Meconium aspiration was associated with significantly heavier lung weights than amniotic fluid aspiration (4 ml/kg, $P < 0.05$ and 6 ml/kg, $P < 0.001$). The resting lung volumes of animals aspirating 6 ml/kg of amniotic fluid were significantly decreased from non-aspirating control values ($P < 0.05$), but were not significantly different from those of the saline aspiration group.

Pressure-volume curves were performed on the 6 ml/kg aspiration groups of amniotic fluid and saline and on all meconium and non-aspirating control animals (Fig. 3). Data from each group were fitted to the equation $y = -\log 1/x$ and compared by analysis of covariance. The curves for the meconium groups were graphed together because they were not significantly different by analysis of covariance. The mean pressure-volume curve of adult animals aspirating amniotic fluid was nearly identical to the curve of control animals. The inflation portions of the mean curves from animals aspirating saline or meconium showed higher opening pressures and were significantly different in comparison with the mean inflation curve from animals receiving amniotic fluid ($P < 0.05$). The deflation portions of the curves were not significantly different among groups.

A composite lung histology score was derived by assigning a value of 0–3+ based on the presence of leukocytes, macrophages, and atelectasis, such that the “worst case” score would be 9+ (Table 2). The mean score of animals aspirating amniotic fluid 6 ml/kg was significantly greater than the non-aspirating controls ($P < 0.05$) due to mild atelectasis in the animals receiving amniotic fluid. This was not significantly different from saline. The histology score of the meconium aspiration 6 ml/kg group was not significantly worse than those aspirating amniotic fluid,

Fig. 1. PO_2 (expressed as % of pre-aspiration values) for 24-h period after aspiration of 4 ml/kg of the three test fluids by adult rabbits.

Fig. 2. PO_2 (expressed as % of pre-aspiration values) for 24-h period after aspiration of 6 ml/kg by adult rabbits.

Table 1. Lung weight, resting volume¹ and mortality of adult rabbits

	n	Deaths	Lung wt/ body wt (g/kg)	Volume/ body wt (ml/kg)
Control	5	0	4.97 ± 0.56	10.6 ± 0.5 ²
Amniotic fluid (AF)				
4 ml/kg	7	0	5.93 ± 0.51	8.9 ± 0.8
6 ml/kg	8	1	5.22 ± 0.40	7.7 ± 0.8
Saline				
4 ml/kg	4	0	6.42 ± 0.73	8.1 ± 1.3
6 ml/kg	5	0	4.79 ± 0.36	9.9 ± 0.9
Meconium				
4 ml/kg	5	1	8.48 ± 1.07 ³	10.1 ± 1.7
6 ml/kg	5	4	9.65 ± 1.36 ⁴	6.9 ± 1.3

¹ Values are at time of spontaneous death or 24 h after aspiration and are ± S.E.M.

² Significantly different from AF 6 ml/kg, $P < 0.05$.

³ Significantly different from AF 4 ml/kg, $P < 0.05$.

⁴ Significantly different from AF 6 ml/kg, $P < 0.001$.

Table 2. Lung histology scores¹ of adult rabbits

Group	Score (S.E.)
Controls	0.13 ± 0.13 ²
Amniotic fluid	
4 ml/kg	0.75 ± 0.25
6 ml/kg	1.64 ± 0.46
Saline, 6 ml/kg	1.00 ± 0.35
Meconium	
4 ml/kg	4.10 ± 0.48 ³
6 ml/kg	2.80 ± 0.58

¹ Based on value of 0–9⁺.

² Significantly different from AF, 6 ml/kg, $P < 0.05$.

³ Significantly different from AF, 4 ml/kg, $P < 0.05$.

Fig. 3. Pressure-volume curves 24 h after aspiration in the amniotic fluid (AF) and saline 6 ml/kg and control animals. Meconium, 4 and 6 ml/kg, were condensed into one group (see text).

which was due presumably to the high early mortality in the meconium aspiration group.

The amniotic fluid was obtained from women whose fetuses were 34–40 wk gestational age. The mean epithelial cell count was 717/mm³ (S.E. 217 and range 15–2370), which is slightly higher than cell counts found by others during this period of gestation (13, 14). Four of the 15 samples were contaminated with red blood cells with a mean cell count on these samples of 34,550/mm³ (range 68–176,000). There was no correlation between the epithelial or red blood cell count and the post-aspiration PO_2 at any time (Fig. 4), nor with any of the other aspects of pulmonary physiology that we measured.

Newborn rabbits. Sixty-one vaginally delivered rabbit pups were studied. One-hundred and fifteen pups were obtained by cesarean delivery, but 30 were excluded because the lung scan demonstrated that the aspiration material had not entered the lungs. Scans in the cesarean animals included in the study demonstrated thorough distribution of the aspiration fluids throughout the lung and that significant amounts of fluid were not displaced into the nasopharynx (Fig. 5).

Mortality (Fig. 6) in animals aspirating amniotic fluid did not differ significantly from those aspirating saline or nothing (Fischer's exact test). Mortality in the meconium aspiration groups at this dose was 100% with death occurring in less than 15 min. The respiratory rates (Figs. 7 and 8) of the amniotic fluid aspiration groups were not significantly different from the saline and non-aspirating control groups, and were similar to previously published values for cesarean delivered rabbit pups (18). Lung weight/body weight ratios and static deflation curves performed at 48 h of age were also not significantly different (Table 3).

Fig. 4. Amniotic fluid epithelial cell count *versus* PO_2 in the animal aspirating that sample at 2 h.

Fig. 5. Technetium 99 scan performed shortly after birth demonstrates thorough distribution of the test fluid throughout the lungs.

Fig. 6. Mortality in the 48 h after aspiration of amniotic fluid, saline, or 10% meconium solution. Controls were sham-injected.

Chest radiographs of the cesarean delivered pups were scored on a 0-6 scale on the basis of the findings present: decreased aeration, focal infiltrates, or atelectasis (Table 4). The results for each item were averaged so that the "worst case" score would be 6+. The mean score of animals aspirating amniotic fluid was not significantly different from that of the control or saline aspiration group, but was markedly different from the mean score of the meconium aspiration group ($P < 0.001$). Animals that aspirated meconium displayed little or no aeration of their lungs. Positive findings in the amniotic fluid aspiration group were usually mild and cleared by 24 h in all cases except one.

Lung histology (Table 5) was evaluated in the cesarean and vaginally delivered pups by the same scoring system used for

adult rabbits. The mean scores of both amniotic fluid aspiration groups were not significantly different from their respective saline and non-aspirating control groups. The cesarean delivered meconium aspiration group had a significantly higher score than the amniotic fluid aspiration pups ($P < 0.025$), almost entirely accounted for by increased atelectasis in the animals aspirating meconium.

DISCUSSION

These findings do not support the hypothesis that human amniotic fluid is a uniquely harmful substance in its effects on pulmonary function. The types of pathology and abnormal phys-

iology we hypothesized might occur with amniotic fluid aspiration were the following: (1) airway plugging by particulate matter that would be indicated by decreased maximal lung volumes, air trapping at 0 cmH₂O pressure, and abnormal chest radiographs and lung histology; (2) increased lung water, which would be indicated by abnormal chest radiographs and increased lung weight (1); and (3) surfactant washout or inactivation, which would be indicated by decreased lung volumes at 5 or 10 cmH₂O pressure.

In adult rabbits, a transient depression of oxygenation associated with mild atelectasis occurred after aspiration of amniotic fluid or saline. No dose-response relationship could be detected between the cell content of the amniotic fluid and aspects of pulmonary physiology that were measured. Microscopic examination of the lungs of the one adult animal that died after aspirating amniotic fluid revealed normal lungs.

The newborn animals displayed remarkably little respiratory compromise after aspirating an amount of amniotic fluid approaching volumes shown to produce substantial mortality in animal studies of drowning (10, 11, 20). Comparable amounts of 10% meconium solution produced a mortality of 100%.

Perinatal aspiration could possibly occur either in the intra-uterine environment as a series of gasps or as an intrapartum event when the contents of the mouth and nasopharynx might be aspirated. We chose a variety of volumes in adult and neonatal animals that would be near the maximum of those aspirated at birth during which time there was not significant asphyxia. The fluid volumes utilized—a mean of 8 ml/kg for the vaginally

Fig. 7. Respiratory rates over 48 h after aspiration in vaginally-delivered rabbit pups.

Fig. 8. Respiratory rates over 48 h after aspiration in cesarean-delivered rabbit pups.

Table 4. Radiology scores¹ of newborn rabbits

Group	Score	
	<2 h age	24–32 h age
Control	0.17 ± 0.11	All normal
Saline	1.20 ± 0.51	All normal
Amniotic fluid	0.71 ± 0.38	0.25 ± 0.26
Meconium	5.67 ± 0.21 ²	

¹ On a scale of 0–6⁺.

² Significantly different from amniotic fluid $P < 0.001$.

Table 5. Lung histology scores¹ of newborn rabbits

Group	Score
Vaginal delivery	
Control	0.33 ± 0.21
Saline	2.17 ± 0.33
Amniotic fluid	1.30 ± 0.20
Meconium	1.60 ± 0.49
Cesarean delivery	
Control	1.94 ± 0.27
Saline	1.78 ± 0.42
Amniotic fluid	1.67 ± 0.37
Meconium	3.00 ± 0.42 ²

¹ On a scale of 0–9.

² Significantly different from amniotic fluid $P < 0.025$.

Table 3. Lung weight/body wt and static deflation characteristics of newborn rabbits

Group	Lung wt/body wt	Max vol (ml/g lung)	% Max lung vol	
			10 cmH ₂ O	0 cmH ₂ O
Vaginal delivery				
Control	0.013 ± 0.001	7.0 ± 0.4	83 ± 1	21 ± 2
Saline	0.015 ± 0.001	5.5 ± 0.5	83 ± 1	23 ± 1
Amniotic fluid	0.015 ± 0.001	6.4 ± 0.4	84 ± 2	22 ± 2
Cesarean delivery				
Control	0.016 ± 0.001	5.7 ± 0.4	84 ± 1	26 ± 1
Saline	0.015 ± 0.001	5.9 ± 0.4	84 ± 1	28 ± 1
Amniotic fluid	0.017 ± 0.001	5.7 ± 0.4	85 ± 1	27 ± 1

delivered pups and 11 ml/kg for the cesarean pups—were much greater than the 3.5 ml/kg estimated to be the maximum amount of fluid that could be inhaled in a single gasp (12).

This model does not allow us to determine whether surfactant washout occurs during a series of intrauterine asphyxial gasps with aspiration of amniotic fluid. Sheldon *et al.* (24) found no decrease in surfactant after fetal lamb lung lavage but did detect a decrease in phosphatidylcholine synthesis, which was postulated to be due to an intrinsic toxic element in the amniotic fluid of sheep. It can be estimated that at least 9 min of asphyxia would be necessary to produce a 90% washout of fetal lung fluid (12). Although the effect of aspiration during asphyxia is a significant issue, this study was intended to model the effects of aspiration on a newborn who did not also experience considerable asphyxia.

This study does not support the contention that aspiration of human amniotic fluid causes significant respiratory compromise. Asphyxia that may accompany aspiration and problems with clearance of fetal pulmonary fluid are more likely factors in neonatal respiratory disease associated with aspiration of uncontaminated amniotic fluid.

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