Persistent pulmonary hypertension of the newborn (PPHN) is a devastating illness characterized by pulmonary hypertension, right to left shunting of blood via the foramen ovale and the ductus arteriosus and a structurally normal heart. In the National Institute of Child Health and Human Development (NICHD) Neonatal Observational Study of PPHN, the incidence (measured among infants delivered in high risk centers only) was 1.9/1,000 live births. A diverse number of processes including hypoxemia may lead to the clinical picture recognized as PPHN (1). Fetal hypoxemia has been shown to occur with maternal tobacco smoke exposure (2,3). We hypothesize that maternal tobacco smoke exposure is a risk factor for PPHN in her newborn.

Cotinine, a metabolite of nicotine, is a useful biological marker for nicotine exposure and is in widespread use to validate self-reported smoking status (4). Cotinine has a half life of 15-40 hr in adults and 37-160 hr in infants (5). Cotinine levels have been used as a measure of passive smoking (6,7). Cotinine levels in maternal serum during the second trimester of pregnancy are more predictive of birthweight than smoking history (8).

We undertook a study to investigate the association between maternal and fetal nicotine exposure and PPHN, using cotinine as a biomarker of exposure.

Methods

Subjects. The study took place at Children’s Hospital Oakland, a referral hospital, from January 1991 through June 1992. PPHN was suspected on the basis of clinical observation of the ability of oxygenation and/or disparity between pre- and postnatal oxygen saturation as assessed by pulse oximetry and confirmed by two-dimensional echocardiography demonstrating a right to left shunt. Patients with PPHN were excluded if any of the following were present: confirmed sepsis, chromosomal abnormality, diaphragmatic hernia, or structural congenital heart defect. A total of 36 infants met criteria for enrollment; three families declined to participate. After informed consent was obtained, 33 families completed a detailed questionnaire of these, 31 newborns had cord blood (19 samples) or newborn blood (12 samples) cotinine concentrations determined.

All study infants required mechanical ventilation. Sixteen (51.6%) also received high frequency ventilation, and 16 (51.6%) were placed on extracorporeal membrane oxygenation. Only 5 infants (16.1%) received mechanical ventilation alone. The study infants’ mean maximum alveolar-arterial oxygen gradient (AaDO2) on a fractional inspired oxygen (FiO2) of 1.0 [AaDO2 = 173 - (Paco2 + PAo2)] where Paco2 is the arterial CO2 pressure and PAo2 is the postductal arterial O2 pressure) was 644.3 ± 16.9 with a range of 614-670 and a median of 644. For 27 of these infants, the mean oxygenation index [OI] (OI = 100 / (Paw / FiO2 - Paco2) where Paw is the mean arterial pressure) at the peak of their disease was 51 ± 39.4 with a range of 11-200 and a median of 41.

A reference comparison group of 49 healthy infants was constructed to be roughly equivalent to the distribution of maternal ethnicity in the PPHN group. Infants were frequency matched by maternal ethnicity from the normal newborn nurseries at two representative referral hospitals to form the group. The reference comparison group was frequency matched on maternal ethnicity because both the incidence of smoking and the rate of nicotine metabolism have been shown to vary with ethnicity (9-11). Matching in a case-control study can introduce selection bias, which itself acts as a confounder (12); the result is that the crude estimate of effect underestimates the correct value. This error can be corrected by treating the matching variable, maternal ethnicity, as a confounder and controlling for it in the analysis. Seven families refused to participate. After informed consent was obtained, 42 families completed the questionnaire and 39 had cord blood cotinine levels determined. The questionnaire was administered by an interviewer regarding exposure to tobacco and other agents during the pregnancy. The T-ACE questions were included in the questionnaire to assess alcohol use (13). The T-ACE questionnaire is a simple and quick method of identifying prenatal risk drinking. It consists of five questions: T) How many drinks does it take to make you feel high? (Score 2 if >2 drinks); A) Have people annoyed you by criticizing your drinking? (Score 1 if yes); C) Have you felt you ought to cut down on your drinking? (Score 1 if yes); and E) Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? (Score 1 if yes). For a total score of >2, the specificity is 89% and sensitivity is 69% at identifying women who are consuming ≥1 oz absolute alcohol per day (13).
Cotinine analysis. Cord blood for the comparison group and either cord blood or earliest available newborn blood from the study infants was obtained from the blood bank at the time of enrollment into the study. Both sources of blood will be referred to as infant’s blood in this paper. Serum or plasma was separated, extracted with methylene chloride, and analyzed for cotinine by gas chromatography-mass spectroscopy (GC-MS) using a Hewlett-Packard 5970 mass selective detector (Mountain View, CA) with a 15 m DB-1 fused silica column (0.25-mm id, 0.25 m film thickness, J & W Scientific, Folsom, CA). The amount of cotinine present in a sample was obtained by determining the ratio of the peak area for the protium form molecular ion to the trideuterium form. The minimum detectable concentration of the plasma cotinine was 1 ng/ml. The GC-MS analyses were done by a blinded investigator. Duplicate samples gave identical results.

Statistical analysis. Graphical and univariate statistics were used initially to describe the data and determine the appropriateness of parametric or nonparametric tests of significance. Nominal variables were described as frequencies, ordinal or nonparametric interval variables were described by medians and ranges, and interval, parametric data are described by means and standard deviations (SD). The sample characteristics of the mothers and the infants were examined to determine if any unanticipated differences between the groups existed. Nominal variables were tested using chi-squared analysis or Fisher’s exact test as appropriate; two sample t-tests were used for normally distributed data, and Mann-Whitney (or two sample Wilcoxon rank sum) tests were used for skewed data. Any variable with a p-value <0.2 was considered for entry into a multivariate model to control for residual confounding.

The association between cotinine levels and disease status was examined in two phases. Cotinine levels <1 are classified by definition as undetected; values >1 were therefore classified as detected, and the overall association was tested first on a nominal scale using chi-square analysis; the result was reported as an unadjusted odds ratio. The continuous portion of the measures of cotinine (those values >1) were compared using the appropriate nonparametric test.

Since matching on a variable known to be associated with the exposure in a case-control study can introduce selection bias (12), logistic regression was used to adjust the odds ratio accordingly, with ethnicity added as an indicator variable. None of the maternal characteristics were considered significantly different according to the above definition and were not included in the model.

Most statistical analyses were carried out on a Gateway 2000 486 microcomputer (N. Sioux City, SD) using STATIT software (Statware, Inc., Corvallis, OR), all running under SCO UNIX. PC software such as SAS (SAS System, SAS Institute, Cary, NC) and SPPlus (Stat-Sci, Seattle, WA) were also used for some specific analyses.

Results

Maternal characteristics are shown in Table 1. As planned, there was no significant difference in the ethnic distribution of the two groups. No significant differences in maternal education, age, gravidity, or parity between the study and comparison families were noted.

Infant characteristics are shown in Table 2. There was no significant difference in birth weight, although the gestational age as determined by estimated date of confinement (EDC) was significantly longer for the PPHN group (40.6 vs. 39.5 weeks; p = 0.0037). This difference is clinically insignificant. When birth weight is corrected for gestational age, there is no significant difference. Apgar scores at 1 and 5 min were significantly lower in the PPHN group as expected.

Maternal report of tobacco use is shown in Table 3. Women were classified as 1) active smokers if they had smoked at any time during pregnancy, 2) passive smokers if they had daily passive smoke exposure until the time of delivery, or 3) never smoked or had quit smoking prior to pregnancy and had minimal passive smoke exposure. Due to the small number of non-smoking women who reported daily passive smoke exposure, the analysis was conducted comparing exposed women (active and passive smoke exposure) versus nonexposed women. There was a borderline statistically significant difference in self-reported smoking between the two groups (p = 0.080). However, due to the small sample size, this study lacks sufficient power to detect a difference of this magnitude (power = 0.50).

### Table 1. Maternal characteristics

| Characteristics       | PPHN (n = 31) | Comparison group (n = 39) | p-value | Test |
|-----------------------|--------------|--------------------------|---------|------|
| Maternal Ethnicity    |              |                          |         |      |
| White                 | 14           | 15                       | 0.805   | χ²   |
| Black                 | 9            | 14                       |         |      |
| Other (Hispanic and Asian) | 8          | 10                       |         |      |
| Gravidity             |              |                          |         |      |
| 1                     | 9            | 9                        | 0.062   | χ²   |
| 2                     | 6            | 11                       |         |      |
| 3 or greater          | 16           | 19                       |         |      |
| Parity                |              |                          |         |      |
| 1                     | 12           | 15                       | 0.774   | χ²   |
| 2                     | 9            | 14                       |         |      |
| 3 or greater          | 10           | 10                       |         |      |
| Maternal education, years (mean ± SD) | 11.8 ± 4.0 | 12.7 ± 4.2 | 0.422 | Mann-Whitney |
| Maternal age, years (mean ± SD) | 30.1 ± 6.3 | 28.6 ± 6.1 | 0.316 | Student's t-test, 2-tailed |

Abbreviations: PPHN, persistent pulmonary hypertension of the newborn; SD, standard deviation.

### Table 2. Infant characteristics

| Characteristics       | PPHN (n = 31) | Comparison group (n = 39) | p-value | Test |
|-----------------------|--------------|--------------------------|---------|------|
| Birthweight, g (mean ± SD) | 3621 ± 669 | 3411 ± 529 | 0.152 | Student's t-test, 2-tailed |
| Gestational age, weeks (mean ± SD) | 40.6 ± 1.6 | 39.5 ± 1.7 | 0.0037 | Student's t-test, 2-tailed |
| Apgar score, 1 min    |              |                          |         |      |
| 0–3                   | 11           | 0                        | <0.0001 | Mann-Whitney |
| 4–6                   | 12           | 2                        |         |      |
| 7–10                  | 8            | 37                       |         |      |
| Apgar score, 5 min    |              |                          |         |      |
| 0–3                   | 4            | 0                        | <0.0001 | Mann-Whitney |
| 4–6                   | 10           | 0                        |         |      |
| 7–10                  | 17           | 39                       |         |      |

Abbreviations: PPHN, persistent pulmonary hypertension of the newborn; SD, standard deviation.
Maternal exposures other than tobacco, which were obtained by questionnaire, are shown in Table 4. Due to the small number of study participants with exposure, dose and timing of exposure were not analyzed. Table 4 represents the number of women who were exposed at least once during the pregnancy to the chemicals listed and their T-ACE scores. No significant differences were observed, with the exception of antinausea preparations.

The cotinine concentrations of the newborn's blood were compared to maternal self-reported smoking status (Fig. 1). Two women who reported no smoking had cord blood cotinine concentrations consistent with active smoking. To determine if our results agreed with external studies, we used the previously published interval values defining cotinine concentration by smoking status: no exposure <1 ng/ml; passive smoke exposure, 1–13.7 ng/ml; and active smoker >13.7 ng/ml (14). We looked at our data by reported smoking status to determine if the cotinine values agreed or disagreed with the literature based intervals. Results are shown in Table 5. There was a significant association between our data and literature-based data (chi-square p = 0.025).

Cotinine concentrations were compared between the infants with PPHN and the comparison group (Fig. 2). Cotinine was detectable in the blood of 64.5% (20/31) study infants and 28.2% (11/39) comparison infants (p = 0.002). The distribution of detectable cotinine concentrations, shown in Figure 2, is clearly higher in the PPHN group than in the comparison group (medians are 5.2 ng/ml for PPHN and 2.0 ng/ml for comparison; Mann-Whitney one-sided p-value = 0.051).

To assess the impact of passive smoke exposure, we reanalyzed the data for both groups excluding active smokers as defined by self report and/or a cotinine concentration >13.7 mg/ml (14). The results are shown in Figure 3. Cotinine was detected in the blood of 50% (11/22) study infants as compared to 18% (6/32) comparison infants (p = 0.015) of apparently nonsmoking women. The distribution of detectable cotinine concentrations, shown in Figure 3, is also significantly higher in the PPHN group (medians are 3.5 ng/ml for PPHN and 1.65 ng/ml for comparison; Mann Whitney one-sided p-value = 0.022). However, these results are based on a small sample size (n = 17).

To correct for any residual confounding due to baseline differences in the groups and any selection bias introduced by the matching method, we performed a logistic regression analysis. The unadjusted odds ratio (OR) was 4.68 (95% CI, 1.679–12.755; p = 0.0086), which is consistent with the contingency analysis table (Fig. 2). Ethnicity was added to the model as indicator variables, and the adjusted OR was 6.10, correcting for the expected bias toward the null. While the use of antinausea medications is associated with the disease, it is not associated with the exposure (Fisher's Exact Test, p = 0.692). In addition, logistic regression analysis of only those patients who did not use this medication resulted in the same odds ratio. Because there was no evidence that the use of antinausea medications confounded the relationship between smoking and PPHN, no further adjustment was necessary. None of the other possible confounding variables met the criterion for entrance into the model (all p-values >0.2).

Discussion

Our results show that cotinine was more likely to be found in the blood of infants with PPHN than in that of comparison infants, and that the cotinine concentrations were significantly higher in the PPHN group than in the comparison group. In addition, to examine the role of passive smoking, active smokers were excluded from analysis. The prevalence of significant concentrations of cotinine was again higher in the PPHN group, suggesting an association between environmental tobacco smoke exposure and PPHN.

**Table 3. Maternal smoking status**

| Exposure status (By questionnaire) | PPHN, n = 31 (%) | Comparison group, n = 39 (%) |
|------------------------------------|-----------------|-----------------------------|
| Nonexposed                         | 19 (61.3)       | 31 (79.5)                   |
| Exposed                            | 12 (38.7)       | 8 (20.5)                    |
| Daily passive                      | 4 (12.9)        | 2 (5.1)                     |
| Active*                            | 8 (25.8)        | 6 (15.4)                    |

Abbreviations: PPHN, persistent pulmonary hypertension of the newborn.

*Smoked any amount during pregnancy.

**Table 4. Maternal exposures**

| Characteristics | PPHN group | Comparison group | p-value, \( \chi^2 \) | \( \chi^2 \) | \( \chi^2 \) |
|-----------------|------------|-----------------|-----------------|---------------|---------------|
| Caffeine*       | 15         | 22              | 0.6307          |               |               |
| Vitamins        | 28         | 37              | 0.6489          |               |               |
| Antacids        | 15         | 11              | 0.1345          |               |               |
| Antinausea     | 7          | 0               | 0.0022          |               |               |
| Antinausea     | 4          | 4               | 1.0             |               |               |
| Antinausea     | 20         | 23              | 0.0852          |               |               |
| Antibiotics     | 5          | 4               | 0.4959          |               |               |
| Alcohol         | 14         | 19              | 0.813           |               |               |
| T-ACE ≥2        | 9          | 5               | 0.1333          |               |               |
| Opiates         | 3          | 1               | 0.3152          |               |               |
| Cocaine         | 2          | 2               | 1.000           |               |               |

Abbreviations: PPHN, persistent pulmonary hypertension of the newborn; FET, Fisher’s Exact Test; NSAID, nonsteroided anti-inflammatory drugs.

**Table 5. Comparison of study data with published values**

| Self-reported category | No. | Cotinine concentration | Agreement (%) |
|------------------------|-----|------------------------|---------------|
| No smoking             | 50  | 34                     | 68            |
| Passive                | 6   | 3                      | 50            |
| Active                 | 14  | 8                      | 65            |
| Overall                | 70  | 45                     | 65            |

Abbreviations: PPHN, persistent pulmonary hypertension of the newborn; ND, not detectable.
There are several possible explanations for our findings. First, cotinine may accumulate in the fetal compartment of compromised fetuses, giving rise to higher cotinine concentrations in the newborn's blood. This is unlikely due to its low ionization constant, $pK_{a1}$ of 4.8. At physiologic or low ionization constant, physiologic pH, it will be predominantly nonionized and thus be able to rapidly diffuse across the placental barrier as shown by Luck et al. (15).

Second, there may be decreased metabolism of cotinine by the PPHN fetuses, but that should not result in higher cotinine concentrations. Because nicotine and cotinine both rapidly equilibrate between the maternal–fetal compartments (15) and the mixed function oxidases have little activity in fetal liver (16), the majority of cotinine and nicotine must be metabolized by the maternal liver. Thus, the cotinine half-life in utero is not dependent on fetal liver metabolism.

Third, the time between the last exposure to tobacco smoke and the blood drawing was shorter for the PPHN group than for the comparison group. This explanation for our findings is unlikely for several reasons. Since we used the first blood obtained after transport of the baby to our hospital in 12 cases, the length of time between last exposure and blood drawing is already biased towards a longer interval for the PPHN infants. Also, the half-life of cotinine in children is 37–160 hr. The interval between last exposure and obtaining cord blood would have to differ between the groups by at least 24 hr to become significant. One explanation for such a delay in the comparison group is that the mothers smoked less, which is consistent with our findings. The other explanation, that these mothers were hospitalized in labor for greater than 24 hr, is not consistent with our data. In our comparison group, no mother had prolonged or difficult labor. In addition, the majority of mothers in our study (50/70) did not report smoking or passive smoke exposure. Therefore, no interval could be obtained from them between their last exposure and time of birth.

Finally, PPHN infants could be exposed to more nicotine while in utero. The only biological source of nicotine is from exposure to tobacco and other nicotine-containing plants. While ingestion of nicotine-containing vegetables may theoretically raise plasma cotinine levels (17), the amount of raw vegetables that would need to be consumed to result in detectable levels of cotinine would require an unusual diet. In addition, there is no reason to assume that the diets of the two groups in this study were different. Thus, the most likely explanation for our findings is that mothers of the infants with PPHN are exposed to more tobacco or tobacco products.

We measured cotinine concentrations in the infants' blood because self-report of smoking or tobacco smoke exposure is known to be unreliable. This is evident in Figure 1 in which cotinine levels exceeded 100 ng/ml in women who denied smoking. In the PPHN group, cord blood was unavailable for some infants. In these cases, cotinine was measured in the first available blood. None of these infants had exposure to nicotine or cotinine through breast milk or passive smoking prior to blood sampling. Therefore, collecting blood from these infants rather than obtaining cord blood should only decrease the concentration of cotinine in their blood.

The prevalence of self-reported active smoking by mothers of the PPHN and comparison groups was 27.3 and 14.3%, respectively. A survey of 29,494 women in California in 1992 found marked ethnic differences between tobacco use by self report (10). Using these ethnic-specific prevalence rates and the known ethnic composition of our groups, the expected prevalence of smoking in the PPHN and comparison groups is 13.3 and 13.6%, respectively. Although the prevalence of self-reported smoking in the PPHN group is almost twice the expected rate, the prevalence was not significantly different from expected by chi-square analysis in either group, although the power of chi-square analysis is low.

The prevalence of smoking varies both with maternal ethnicity and socioeconomic status. A comparison group was constructed to be similar in ethnic representation, with women from the same geographic area. Educational level has been widely used as an indicator of socioeconomic level (18,19). The educational level of PPHN and comparison group mothers was obtained by questionnaire and found to be the same in both groups. Thus, the study and comparison groups would be expected to have a similar prevalence of smoking.

The characteristics of the infants in the PPHN and comparison groups differed in Apgar scores. Lower Apgar scores are known to be associated with PPHN and thus would be expected to be lower in the PPHN group relative to the comparison group (20,21).

In the only other published study investigating the etiology of PPHN, self-reported use of aspirin, nonsteroidal anti-inflammatory drugs (NSAID), illicit drugs, and tobacco products were associated with PPHN (22); only aspirin and NSAID use remained statistically significant in multivariate analysis. However, this study did not attempt to ascertain passive smoke exposure, nor were biochemical markers of exposure used. In contrast, we obtained a detailed exposure history from each study participant. We found no statistical difference in exposure to aspirin and NSAID or to cocaine. However, the numbers of women exposed were small in both groups, with low power to distinguish small differences in exposure between the two groups. We did find antinausea prescription drug use solely in the PPHN group. The use of antinausea prescription drugs should be considered in future studies of the etiology of PPHN to more fully delineate their possible role.

We are confident that the infants included in the PPHN group represent a relatively homogenous group. With the difficulty in establishing the diagnosis of PPHN (23), we used strict criteria for inclusion into this study. Only patients with both a diagnosis of PPHN by the attending neonatologist and a right to left shunt demonstrable on echocardiogram were included for study. These patients represent critically ill newborns with large AaDO2 and OI, with nearly half receiving extracorporeal membrane oxygenation. Therefore, both active and passive maternal exposure to tobacco smoke is a risk factor for PPHN. We encourage pregnant women to cease smoking and to avoid exposure to second-hand tobacco smoke.

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Figure 3. The distribution of cotinine concentrations of both comparison ($n = 32$) and PPHN ($n = 22$) infants after exclusion of mothers who are active smokers either by self report or by an infant blood cotinine concentration greater than 13.7 ng/ml. Abbreviations: PPHN, persistent pulmonary hypertension of the newborn; ND, not detectable.
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