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**I. SUMMARY**

On August 15, 1989, the National Institute for Occupational Safety and Health (NIOSH) received a request for a health hazard evaluation regarding occupational exposures to aerosolized ribavirin at Florida Hospital in Orlando, Florida. The request was submitted by the hospital management in response to concerns about a perceived cluster of miscarriages among employees working on the pediatrics unit. In interviews with pediatric staff, estimates of the number of miscarriages ranged from 5 of 8 pregnancies to as high as 9 of 12 pregnancies (63-75%). No additional information was available regarding confounding exposures or other adverse reproductive effects, such as reduced fertility, in the affected women.

In response to this request, two avenues of investigation were followed. Employee exposures to aerosolized ribavirin were documented by both environmental monitoring and biological monitoring; the results of these investigations and recommendations for reducing exposure were presented in a previous health hazard evaluation report.<sup>1</sup>

The other investigation was an epidemiologic study to test for an association between occupational exposure to ribavirin and the occurrence of either spontaneous abortion or decreased fertility. A retrospective questionnaire study was conducted of employees who were and were not exposed to ribavirin. The potentially exposed population consisted of women who worked on the pediatrics floor at Florida Hospital as nurses or respiratory therapists. The unexposed comparison group was composed of nurses who worked on medical and surgical floors where ribavirin was not used. Because of the possible confounding effect of occupational exposures to chemotherapeutic drugs, which have a known association with spontaneous abortions, nurses working on oncology floors were not included in the comparison group.

Of the 528 questionnaires which were mailed, 273 completed questionnaires (52%) were received, of which 228 were completed by women. When asked to summarize their entire reproductive histories, 155 of these women had been pregnant at least once, and 39 women reported having at least one miscarriage. Thus, 25% of the women respondents who had ever been pregnant reported having at least one miscarriage. In all, 383 pregnancies were reported, of which 55 (14%) ended in a miscarriage. During the time when ribavirin was in use in the hospital there were 64 completed pregnancies, of which 61 ended in a live birth and 3 (4.7%) ended in a spontaneous abortion. Among the 22 women who reported ribavirin exposure there were 27 pregnancies of which one ended in a spontaneous abortion. Among the 33 women who reported no ribavirin exposure, there were 37 pregnancies of which two ended in a spontaneous abortion. The number of spontaneous abortions reported was too small to permit any meaningful statistical analysis.

The reported number of cycles needed to achieve pregnancy was compared between women who were exposed to ribavirin at the time they were trying to conceive and those who were not exposed to ribavirin. There was no significant difference in the time to pregnancy in the two groups ( $p=0.29$ ).

There are several reasons to believe that the responses to our survey resulted in undercounting of miscarriages during the study period. The small numbers of spontaneous abortions during the period of interest make it impossible to draw any conclusions about the risk of spontaneous abortion associated with occupational exposures to ribavirin. The data do not show an association between ribavirin exposure and an increased time to achieve pregnancy, although the power to detect such an association was reduced by the small number of pregnancies.

**KEYWORDS** SIC 8062 (General Medical and Surgical Hospitals), ribavirin, Virazole®, 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboximide, aerosolized drugs, aerosolized pharmaceuticals, health care workers, aerosol containment system, spontaneous abortion, reproduction.

## II. INTRODUCTION

On August 15, 1989, the National Institute for Occupational Safety and Health (NIOSH) received a request for a Health Hazard Evaluation regarding occupational exposures to aerosolized ribavirin at Florida Hospital. The request was submitted by the hospital management in response to concerns about a perceived cluster of miscarriages among employees working on the pediatrics unit.

In October 1987 Florida Hospital began the use of aerosolized ribavirin for treatment of pediatric cases of respiratory syncytial virus (RSV) pneumonia. In 1988 the hospital instituted the use of body substance isolation procedures for patients receiving ribavirin therapy, including personnel use of gloves, gowns, and masks. The hospital began use of the ICN Aerosol Delivery Hood in September 1989.

Between approximately May 1988 and May 1989, several pregnancies of nurses working on the pediatric floor ended in spontaneous abortions. The exact number of spontaneous abortions is uncertain; in interviews with pediatric staff, estimates of the number of miscarriages ranged from 5 of 8 pregnancies to as high as 9 of 12 pregnancies (63-75%). No additional information was available regarding confounding exposures or other adverse reproductive effects, such as reduced fertility, in the affected women.

In response to this request, two avenues of investigation were followed. Employee exposures to aerosolized ribavirin were measured with both environmental monitoring and biological monitoring. Samples were collected over several visits, during which time assessments were made of various changes in engineering controls, work practices, and personal protective equipment. Creatinine-corrected post-shift urinary ribavirin values ranged from <0.001 to 0.140 micromoles of ribavirin per gram of creatinine ( $\mu\text{mol/g}$ ), with a mean of 0.017  $\mu\text{mol/g}$ . The mean post-shift value for nurses was 0.030  $\mu\text{mol/g}$  while the mean for RTs was 0.004  $\mu\text{mol/g}$ . Forty-six full-shift and short-term personal air samples for AR were collected from nurses and RTs. Fifty area air samples were collected. Among nurses, full-shift personal samples ranged from 18.7 to 31.0 micrograms per cubic meter ( $\mu\text{g/m}^3$ ) during administration with the Aerosol Delivery Hood® (ADH) alone, non-detected to 13.2  $\mu\text{g/m}^3$  for the ADH enclosed by the Demisitifer® scavenging tent, 12.0 to 28.2  $\mu\text{g/m}^3$  for the croup tent, and <3.3 - 4.8  $\mu\text{g/m}^3$  for the ventilator. Air sampling results demonstrated that engineering controls and appropriate work practices can appreciably reduce health care workers exposures to aerosolized ribavirin. The finding of detectable concentrations of ribavirin in the urine demonstrates the need to use effective engineering

controls and to strictly adhere to good work practices. These investigations have previously been reported to Florida Hospital employees and management.<sup>1</sup>

The other investigation, the subject of this report, was an epidemiologic study to test for an association between occupational exposure to ribavirin and the occurrence of spontaneous abortion. A retrospective questionnaire study was conducted of employees who were and were not exposed to ribavirin.

### III. BACKGROUND

The medical administration of pharmaceutical aerosols is rapidly expanding. Asthma, chronic obstructive pulmonary disease, and pulmonary infections are frequently treated with aerosols of sympathomimetics, beta-agonists, corticosteroids, and antimicrobials. The advantages to the patient include rapid onset of therapeutic action, optimized delivery of the drug to the site of action, and reduction in unwanted systemic side-effects. Aerosol delivery methods, however, can result in exposures to the health care worker (HCW). The difficulty in controlling the spread of aerosols, along with their small particle size, contributes to the risk of occupational exposure.

Much of the concern about occupational exposure to pharmaceutical aerosols has centered on the use of ribavirin. The adverse reproductive effects of ribavirin exposure in animal studies have raised concerns among HCWs who administer ribavirin, many of whom are in their reproductive years. However, no published studies have linked ribavirin to fetal abnormalities or fetal loss in humans.

In previous studies, ribavirin has not been consistently detected in body fluids of HCWs.<sup>2,3,4</sup> The lack of data demonstrating uptake of the drug following occupational exposure has raised questions as to the extent of the potential health risk posed by ribavirin.<sup>5,6</sup> Differing opinions regarding the need for ribavirin-exposed HCWs to wear personal protective equipment have been expressed in the scientific literature. In its "Aerosol Consensus Statement-1991," the American Association for Respiratory Care recommended that HCWs wear full barrier protection including respirators.<sup>7</sup> In contrast, the American Academy of Pediatrics stated in its "Ribavirin Therapy for Respiratory Syncytial Virus" policy that the use of gloves and gowns is unnecessary, and "...the use of a mask designed to block absorption of particulate droplets with ribavirin might provide added protection."<sup>5</sup> No occupational exposure criteria for ribavirin have been published by the Occupational Safety and Health Administration (OSHA), NIOSH, or the American Conference of Governmental Industrial Hygienists (ACGIH).

NIOSH has, however, offered recommendations to minimize ribavirin exposure of HCWs and other individuals who may enter rooms where ribavirin is administered.<sup>1</sup>

#### *Uses of Ribavirin*

Ribavirin is a synthetic nucleoside that is licensed by the U.S. Food and Drug Administration (FDA) for the short-term treatment of severe respiratory syncytial virus (RSV) infections.<sup>8</sup> Its antiviral activity is thought to result from inhibition of RNA and DNA synthesis, which subsequently inhibits protein synthesis and viral replication.<sup>9</sup> Ribavirin has also been used to treat both influenza B pneumonia and RSV pneumonia in immunocompromised adults.<sup>10,11</sup> Clinical trials have studied the use of ribavirin in the treatment of influenza in otherwise healthy adults.<sup>12,13</sup>

Ribavirin is commercially available as a sterile, lyophilized powder, which is initially reconstituted by injecting additive-free sterile water into a vial containing six grams of ribavirin. The initial solution is transferred to a sterile wide-mouthed flask, which serves as the reservoir for the aerosol generator and is further diluted to a final volume of 300 milliliters (mL) [20 milligrams (mg) per mL].

Ribavirin aerosol is generated by a Small Particle Aerosol Generator® (Model SPAG-2® nebulizer) marketed by the drug manufacturer (ICN Pharmaceuticals, Inc, Costa Mesa, California). The SPAG-2® nebulizer delivers AR at a rate of approximately 14 liters per minute (L/min). According to the manufacturer, when the recommended starting solution of 20 milligrams of ribavirin per milliliter (mg/mL) sterile water is used, the average concentration of aerosol generated by the unit is expected to be 190 milligrams per cubic meter (mg/m<sup>3</sup>).<sup>14</sup> The small particle size of the ribavirin aerosol (1.0-1.3 micrometer mass median aerodynamic diameter) permits deep penetration of the drug into the patient's lungs.

The aerosol can be delivered to the patient by a variety of methods, including face mask, head hood (i.e. Aerosol Delivery Hood®), croup or mist tent, oxygen hood, or direct coupling to tracheostomy. During these applications, aerosol may escape into the environment and be inhaled by hospital staff caring for the patient or working nearby.

*Use of Ribavirin at Florida Hospital*

In October 1987 Florida Hospital began the use of aerosolized ribavirin for treatment of pediatric cases of respiratory syncytial virus (RSV) pneumonia. In 1988 the hospital instituted the use of body substance isolation procedures for patients receiving ribavirin therapy, including personnel use of gloves, gowns, and masks. The hospital began use of the ICN Aerosol Delivery Hood in September 1989. Since that time the hospital has implemented other control measures including: ventilation controls; the use of negative-pressure containment tents; the use of personal protective equipment including isolation gowns, shoe covers, latex gloves, a cap, and high efficiency particulate air (HEPA) disposable respirators with qualitative respirator fit testing; and guidelines for work practices to reduce exposures.

IV. METHODS

A. Overview

Concerns were expressed about the possible association between ribavirin exposure and adverse reproductive effects among the nurses at Florida Hospital. The NIOSH investigation addressed these concerns by exploring two questions:

- 1) Were the pregnancies of women who were occupationally exposed to ribavirin more likely to end in spontaneous abortion than those of unexposed women?
- 2) Were women who were occupationally exposed to ribavirin more likely to experience difficulty in becoming pregnant than unexposed women?

To address these questions, a study was designed in which women reportedly exposed to ribavirin during a defined period were surveyed by the use of a mailed questionnaire, as was a comparison population of nurses without ribavirin exposure. The rate of spontaneous abortions in the two groups was to be compared. Second, difficulty in becoming pregnant would be assessed by comparing the time required to achieve pregnancy between women with and without reported ribavirin exposure.

The study population consisted of women who worked on the pediatrics floor at Florida Hospital as nurses or respiratory therapists during the period from January 1, 1987 - March 31, 1990. This study period was selected to capture the entire interval from the time ribavirin was introduced to the time of the investigation, and represented an attempt to examine the time period before

and after a reported cluster of miscarriages. The names and addresses of nurses and respiratory therapists who worked on the pediatrics floor during this period were obtained from hospital employment records. The unexposed comparison group was composed of nurses who worked on medical and surgical floors where ribavirin was not used. Because of the possible confounding effect of occupational exposures to chemotherapeutic drugs, which have a known association with spontaneous abortions, nurses working on oncology floors were not included in the comparison group.<sup>15</sup>

Florida Hospital supplied the names of 535 current and former employees in three employment categories: 121 (22.6%) pediatric staff, including nurses, aides, and clerical staff; 185 (34.6%) respiratory therapy staff, and 229 (42.8%) nurses from the comparison group. Addresses were not available for 7 respiratory therapists, so questionnaires were mailed to 528 employees.

#### B. Spontaneous Abortion

Each woman thus identified was asked to complete a mailed questionnaire asking about reproductive history and ribavirin exposure history (see Appendix). Respondents were asked about other exposures which might affect reproductive outcome, such as age at pregnancy, illnesses, smoking, and alcohol use. The questions about reproductive history asked how many times the respondent had ever been pregnant, and how many of these pregnancies had ended in miscarriages. Respondents were then asked to complete a more detailed page of information for each pregnancy since January 1, 1987, including pregnancies which had begun earlier but were still in progress on January 1, 1987. If a pregnancy did not end in a live birth, respondents were asked if the pregnancy had ended in a miscarriage, ectopic pregnancy, or an induced abortion (the questionnaire did not ask for the reason for an induced abortion). If the pregnancy had ended in a miscarriage, questions were asked to determine if the pregnancy had been lost due to reasons which were highly unlikely to be related to an occupational chemical exposure. These reasons included infection, cervical incompetence, and physical trauma. If the pregnancy loss could not be explained by the causes listed, it was considered a case of spontaneous abortion and was included in the study analysis as such.

The mean half-life of ribavirin in serum has been reported as 52 hours (late elimination phase).<sup>16</sup> After seven half-lives, over 99% of a drug will be eliminated; in this case, seven half-lives is 15 days. An additional two weeks was added to account for the uncertainty associated with calculations based on reported menses. A pregnancy with ribavirin exposure was therefore defined as one with a reported ribavirin exposure anytime in the period from

one month before estimated time of conception until the end of the first trimester. Each conception time was estimated by subtracting the reported number of weeks the pregnancy lasted from the reported date the pregnancy ended; the first trimester was estimated by adding 13 weeks to the estimated conception time.

#### C. Difficulty in conceiving (time to pregnancy)

In the study of potential environmental effects on reproduction in females, spontaneous abortion measures only one effect - the loss of a recognized pregnancy. However, many pregnancy losses occur before the pregnancy has been recognized by the woman. In one study, women volunteers submitted daily urine specimens for measurement of human chorionic gonadotropin (hCG) as an early marker of pregnancy; 22% of all pregnancies detected by hCG failed to survive to the stage of being recognized clinically.<sup>17</sup> If this rate were increased by an environmental exposure, it would not be obvious to the women affected. In addition, an environmental exposure could interfere with reproductive function by impeding ovogenesis, ovum transport, fertilization, or zygote implantation, thereby preventing a pregnancy from developing. A measure of loss of recognized pregnancies would not detect these effects.

Despite the potential obstacles to successful pregnancy, in each menstrual cycle approximately 25% of healthy couples trying to achieve pregnancy will successfully produce a recognized conception. Less fecund couples will be less successful, and will be less likely to produce a recognized pregnancy in a given number of menstrual cycles. A measure of this difference is the number of nonconceiving cycles each couple requires to conceive. A short series of questions has been developed and used to assess the number of cycles required to achieve pregnancy; this number of cycles has been termed the "time to pregnancy."<sup>18,19</sup> These questions were included in the questionnaire in order to compare the time to pregnancy for women occupationally exposed to ribavirin to the time to pregnancy for women not exposed.

#### D. Analysis

Completed questionnaires were coded and the responses were transcribed into data files for computer-based analysis. The statistical analysis of the responses was performed using SAS version 6.08 for OS/2-based personal computers (SAS Institute, Cary, NC).

V. RESULTS

A. Response rates

Questionnaires were first mailed in May 1991, and 185 were completed and returned by the addressees. A second copy of the questionnaire was mailed in September 1991 to those who did not respond, and 89 additional completed questionnaires were received. In both mailings, questionnaires which were returned by the post office with new forwarding addresses were mailed to the new address. Of the 528 questionnaires which were mailed, 273 completed questionnaires (52%) were received, 70 (13.3%) were returned by the post office as undeliverable, and 185 (35%) were not returned. We assume that all 458 questionnaires which were not returned by the post office were delivered to addressees. When considering only those 458 questionnaires, questionnaires were completed and returned by 69 of 110 (63%) of the pediatric staff, 86 of 133 (65%) of the respiratory therapists, and 118 of 215 (55%) of the nurses from the comparison group. The response rates among the 3 employment groups did not significantly differ ( $p=0.15$ , chi square test).

Interestingly, 45 of 178 (25%) questionnaires addressed to respiratory therapists were returned by the post office as being undeliverable. This was significantly more than the 11 of 121 (9%) questionnaires addressed to the pediatrics staff and the 14 of 229 (6%) addressed to the comparison group ( $p=0.00000003$ , Chi square test). The reason for this differential is unknown, although it may be that the population of respiratory therapists is more mobile than the other two groups, resulting in a greater likelihood of expired forwarding addresses. The effect of this difference on our study also cannot be determined. In the environmental measurements of occupational exposures of respiratory therapists and nurses at Florida Hospital, respiratory therapists had exposures of higher magnitude but of shorter duration, resulting in lower time-weighted average exposures and less absorption of ribavirin.<sup>1</sup> Exposures were not measured in the investigation we report here, but were scored as "exposed" or "unexposed" based on self-reported data. The relative absence of respiratory therapists would bias the "exposed" group towards the inclusion of women with higher exposure levels. If occupational exposure to ribavirin was dose-related to an adverse reproductive effect, the study might be more likely to show that adverse effect under these circumstances.

The clinical definition of infertility is an inability to conceive after one year of noncontracepting intercourse. Assuming a typical menstrual cycle of 28 days, this represents a period of 13 cycles. After the diagnosis of infertility is made, a woman is more likely to receive medical interventions in an attempt to

achieve pregnancy. In order to free the analysis from a confounding effect of medical intervention, all periods greater than 13 cycles were right censored to be analyzed as 13 cycles.<sup>20</sup>

#### B. Spontaneous abortions

Two hundred twenty-eight of the questionnaires were completed by women. Of these women, 155 had been pregnant at least once (including the time preceding the study period); the mean number of pregnancies per woman was two (range one to nine). Thirty-nine women reported having at least one miscarriage (range one to four). Thus, 25% of the women who had ever been pregnant reported having at least one miscarriage. In all, 383 pregnancies were reported, of which 55 (14%) ended in a miscarriage.

A pregnancy which occurred during the study period was defined as a pregnancy in the period that began January 1, 1987 (including pregnancies which started before January 1 but ended in 1987), and concluded by the time the respondent completed the survey. This period was used to maximize the number of exposed and unexposed pregnancies for which data could be collected from the questionnaires. Using this definition, there were 78 pregnancies occurring during the study period. Eleven of these pregnancies were still in progress at the time the woman completed the survey. One pregnancy was terminated because it was an ectopic pregnancy, and two were terminated by induced abortion. This left 64 epidemiologically analyzable pregnancies, of which 61 ended in a live birth and three ended in spontaneous abortions. This yielded a spontaneous abortion rate of 4.7%.

Among the 22 women who reported ribavirin exposure there were 27 pregnancies of which one ended in a spontaneous abortion. Among the 33 women who reported no ribavirin exposure, there were 37 pregnancies of which two ended in a spontaneous abortion. One woman had one pregnancy with ribavirin exposure and one pregnancy without ribavirin exposure; each pregnancy ended in a live birth.

Because of the small number of spontaneous abortions in the exposed and unexposed groups, no further analysis of spontaneous abortion data was performed. Although the original study design called for the use of hospital treatment records and personnel records to verify an employee's exposure to ribavirin, the small number of spontaneous abortions reported did not merit such an investigation.

### C. Difficulty in conceiving (time to pregnancy)

For analysis of the time to pregnancy data, all reported pregnancies in which contraception was not being used were included in the analysis regardless of outcome. Of the 78 reported pregnancies, there were 60 pregnancies in which the respondents completed the necessary information and were not using contraception during the period before the pregnancy was conceived. Twenty-seven of these pregnancies were conceived during ribavirin exposure. The exposure status of all of the women was constant for the duration of non-contracepting intercourse; in other words, no one was exposed to ribavirin for only part of the time she was trying to become pregnant. In the unexposed group there were four pregnancies with more than 13 cycles (these were 22, 24, 33, and 36 cycles) before achieving a recognized pregnancy, while in the exposed group there were two pregnancies with more than 13 cycles (16 and 40 cycles).

The reported number of cycles needed to achieve pregnancy was compared between women who were exposed to ribavirin at the time they were trying to conceive and those who were not exposed to ribavirin. The reports were analyzed by logistic regression using a Cox proportional hazards model modified for discrete outcome data controlling for maternal age at the calculated date of conception and for maternal race. In this analysis, there was no significant difference between the time to pregnancy in the two groups ( $p=0.29$ ).

## VI. DISCUSSION

### A. Spontaneous abortions

Although there are research data which indicate that ribavirin has adverse reproductive effects in some animal species, there is little information about reproductive effects in women who have been exposed. It was originally our hope that we could study the experience of women who had worked at Florida Hospital in order to gain better understanding of whether there was a risk of adverse reproductive outcomes in association with occupational exposure to ribavirin. The extended length of the study period actually included two time intervals: the period when little was known about occupational exposures and little was done to control them (from 1987, when the drug was introduced, to 1989), and from mid-1989 onwards, when Florida Hospital began its program of installing engineering controls and protective equipment to reduce exposures.<sup>1</sup>

The expected rate of spontaneous abortion is approximately 15-20% of pregnancies, depending on the age distribution of the women in the group under study.<sup>21</sup> The rate of miscarriage in all pregnancies reported by our survey population was 14%, which closely corresponds with expectations (if one assumes that each miscarriage was a spontaneous abortion, and not a fetal loss due to causes such as infection, trauma, incompetent cervix, etc). In contrast, during our defined study period there were only three spontaneous abortions among 64 pregnancies, an incidence of 4.7%. The small numbers of spontaneous abortions reported by both the exposed and unexposed respondents make it impossible to perform any meaningful comparisons or to draw any conclusions about the risk of spontaneous abortion associated with occupational exposures to ribavirin.

There are several reasons to believe that the responses to our survey resulted in undercounting of miscarriages during the study period. First, it is unlikely that the population of women employed at Florida Hospital has experienced a two-thirds reduction in the rate of miscarriages during the study period, especially since the rate of miscarriages in all pregnancies (including those prior to the study period as well as those during the study period) so closely approximated expected rates of spontaneous abortions. Second, the original request for this hazard evaluation was prompted by a perceived cluster of miscarriages among pediatrics staff; during interviews employees estimated that there had been five to nine miscarriages since ribavirin therapy was instituted. While it is possible that employees overestimated the number of miscarriages, it seems unlikely that the single miscarriage during ribavirin exposure that was reported in this survey was the only actual miscarriage among the pediatrics staff. It is puzzling, however, to note that based on expected rates, it seems that the underreporting was confined to miscarriages in the study period, whereas the rate of miscarriages was as expected during the overall time period. We have no way to determine the reasons for this discrepancy.

It may be asked why we did not directly contact the pediatrics staff to ask for the names of the women who had miscarriages, and thereby make certain that their completed questionnaires were included in the analysis. In conducting an epidemiologic study of this sort, it is very unusual to get responses from 100% of those being surveyed. For that reason, the design must be such that it will be equally likely to find the outcome being studied (miscarriages in this study) in the exposed and unexposed populations. If a woman with ribavirin exposure and a woman without ribavirin exposure both had pregnancies that ended in miscarriage, the study should be designed so that the likelihood of finding the exposed miscarriage and that of finding the unexposed miscarriage are about the same. This assures that the data collected will accurately

represent the odds of miscarriage in both groups. We chose not to perform more aggressive searches for the exposed miscarriages of which we had been told because it would have resulted in better ascertainment of miscarriages in the pregnancies of women with ribavirin exposure than those without. We could not perform the same sort of active search among women without ribavirin exposure because we initially knew nothing about those pregnancies. It would therefore have been more likely that we would "find" miscarriages among exposed women, and the study would have been biased towards the conclusion that ribavirin was associated with miscarriages, whether or not that was true. Such a bias would have invalidated the conclusions of the study.

#### B. Time to pregnancy

In this population we found no evidence that women with occupational exposure to ribavirin were more likely to experience an increased time required to achieve a recognized pregnancy. This result is encouraging, but should be interpreted with caution given the limited number of pregnancies that were available for study; in this situation where roughly half the pregnancies occurred during exposure, the study had only about a 50% chance of detecting an association between exposure and a doubling in time to pregnancy. Thus, there is a 50% chance that this investigation might fail to detect that effect if it were really present. A similar investigation with a larger number of pregnancies would have a greater power.<sup>18</sup>

### VII. CONCLUSIONS

Because of the small number of reported pregnancies ending in miscarriage during the study period, it is not possible for us to reach a conclusion about the association of ribavirin with spontaneous abortions. The fact that we are unable to reach such a conclusion does not prove that ribavirin is or is not an occupational reproductive hazard; the available data do not support either conclusion. The data we collected do not show an association between ribavirin exposure and an increased time to achieve pregnancy.

### VIII. RECOMMENDATIONS

In the absence of new findings, it is prudent to base the need for recommendations upon the existing animal data, which has been reviewed earlier in this report. Recommendations for controlling occupational exposure to ribavirin were conveyed in a previous health hazard evaluation, and many have already been implemented by Florida Hospital.<sup>1</sup> For convenience they are repeated here:

1. Training programs should be developed to educate health care workers about potential risks of ribavirin exposure. Education should not be limited to direct care personnel, but should include ancillary personnel such as phlebotomists, housekeepers, maintenance staff, and others who enter the room during treatment or must clean contaminated rooms, waste, and bedding. The staff should be educated to recognize situations that could result in increased occupational exposure. Female HCWs who are pregnant, lactating, or who may become pregnant, and male HCWs whose sexual partner is not actively avoiding pregnancy should be counseled about risk reduction strategies, such as alternate job assignments. Family members and visitors, who may stay in the room for long periods of time during treatment, should be notified of potential health effects to ribavirin.
2. Various ribavirin administration and scavenging systems result in different levels of environmental contamination. All administration systems should include a mechanism to reduce environmental exposures to ribavirin. It is the responsibility of hospital management to implement more effective control measures as they become available. Administration and scavenging equipment should be inspected by respiratory therapy staff on a regular basis.
3. Rooms where ribavirin is administered should conform to the American Institute of Architects recommendations for isolation rooms.<sup>22</sup> Rooms should provide a minimum of six total air changes per hour, and should be under negative pressure. Room air should be exhausted to the outside rather than recirculated to other areas of the hospital. At Florida Hospital the air from the specially designed isolation rooms is reportedly exhausted to the outside.
4. Air pressure in the ribavirin treatment rooms should be evaluated before therapy begins and daily thereafter. Ideally, ribavirin treatment should begin only if room air pressure is negative with respect to the hallway. This can be accomplished by observing the direction of airflow at the doorway by holding a piece of tissue paper at the cracked doorway.
5. The aerosol generator should be turned off for a minimum of five minutes prior to the HCW entering the room to provide routine care (unless urgent or emergent problems require immediate access to the patient). This could be accomplished by placement of a remote switch outside the room.

6. During aerosol therapy, ribavirin precipitate is deposited on the patient and on the surrounding area. To prevent the dust from becoming airborne, care should be taken when ribavirin-contaminated clothing, bedding, or equipment is handled.<sup>23</sup> Although dermal absorption is not thought to be significant, dermal exposure should be avoided to prevent unintentional oral ingestion or ocular contact. The use of personal protective equipment, including gloves, gowns, and air-tight goggles should be considered.
7. Ribavirin has been found to deposit on contact lenses, so HCWs should be discouraged from wearing lenses when working with ribavirin.<sup>24</sup> If contacts are worn, air-tight goggles should be used.<sup>25</sup>
8. Individual hospitals may choose to use respirators to further reduce HCW exposure to ribavirin. NIOSH/MSHA-approved high efficiency particulate half-mask respirators, assigned to HCWs based on the results of quantitative fit tests, were found by in-mask sampling to reduce exposure to aerosolized ribavirin to the analytical limit of detection.<sup>26</sup> OSHA standard (29 CFR 1910.134) requires that all occupational respirator use must take place within the context of a respiratory protection program that includes evaluation of worker fitness to use a respirator, training, fit testing, and maintenance. Surgical masks should not be relied upon to provide personal protection from occupational exposure to ribavirin.<sup>27</sup>

Disposable respirators, such as the 3M 9970® respirator, have an assigned protection factor of five.<sup>28</sup> The assigned protection factor is the minimum anticipated protection provided by a properly functioning respirator to a given percentage of properly fit-tested and trained users. A respirator with an assigned protection factor of five will presumably reduce the exposure for most wearers five-fold. Florida Hospital's respiratory protection policy specifies a qualitative saccharine fit-test; therefore, the assigned protection factor for respirators when used in conjunction with this type of fit-testing is five. However, it should be noted that a substantial percentage of persons using a particular type of respirator may not achieve an adequate face to face seal fit.<sup>26</sup> On the other hand, a portion of workers using a particular type of respirator will achieve a superior face seal fit, resulting in actual worker protection factors greater than five.

9. In order to help reduce exposure of HCWs to ribavirin, medically unnecessary use of it should be avoided. Accordingly, medical staff should remain mindful of the American Academy of Pediatrics recommendations and other current knowledge regarding ribavirin therapy.<sup>5</sup>

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