

# The Ribavirin Pregnancy Registry: An Interim Analysis of Potential Teratogenicity at the Mid-Point of Enrollment

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## Abstract

**Introduction** Significant teratogenic effects have been demonstrated in all animal species exposed to ribavirin. Ribavirin is prescribed for chronic hepatitis C and is contraindicated in women who are pregnant and in the male sexual partners of women who are pregnant. Both sexes are advised to avoid pregnancy for 6 months after exposure. The Ribavirin Pregnancy Registry was established in 2003 to monitor pregnancy exposures to ribavirin for signals of possible human teratogenicity.

**Methods** This voluntary registry enrolls pregnant women with prenatal exposure to ribavirin. Exposure is classified as direct—women taking ribavirin during pregnancy or the 6 months prior to conception—or indirect—women exposed through sexual contact, 6 months prior to or during pregnancy, with a man who is taking or has taken ribavirin in the past 6 months. Women are followed until delivery and infants for 1 year. When enrollment is complete, birth defect rates will be compared with the Metropolitan Atlanta Congenital Defects Program's

published rate of 2.67. Using data collected since inception in 2003 through February 2016, preliminary rates were calculated.

**Results** The registry has enrolled 272 pregnant women, with 180 live births: there were seven birth defect cases among 85 directly exposed women [7/85 (8.2%) (95% confidence interval (CI) 3.4–16.2)] and four birth defect cases among 95 indirectly exposed women [4/95 (4.2%) (95% CI 1.2–10.4)]. Of the 11 infants, nine had structural defects and two had chromosomal anomalies. Patterns suggesting a common etiology or relationship with ribavirin exposure are not seen.

**Conclusion** Based on the patterns of birth defects reported, preliminary findings do not suggest a clear signal of human teratogenicity for ribavirin. However, the current sample size is insufficient for definitive conclusions, and ribavirin exposure should be avoided during pregnancy and during the 6 months prior to pregnancy, in accordance with prescribing information.

**Clinical Trial Registration** ClinicalTrials.gov identifier: NCT00114712.

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## Key Points

Ribavirin is contraindicated in pregnant women and in male sexual partners of women who are pregnant; however, despite product label warnings, pregnancies continue to occur in women exposed to ribavirin.

Preliminary findings from the Ribavirin Pregnancy Registry do not suggest a clear signal of human teratogenicity for ribavirin; however, the current sample size is insufficient for definitive conclusions.

Slow enrollment has delayed the accrual and dissemination of evidence needed to inform practice. Healthcare providers in the USA are encouraged to report all pregnancies to the registry following direct or indirect ribavirin exposure.

## 1 Introduction

### 1.1 History of the Registry

In 1998, Schering-Plough initiated the formation of an independent pregnancy exposure registry in response to a US Food and Drug Administration (FDA) post-marketing commitment to monitor and evaluate the safety of Rebetol<sup>®</sup> (ribavirin) during pregnancy [1]. A second ribavirin product from Hoffman-La Roche, Copegus<sup>®</sup> (ribavirin) [2], was approved by the FDA in 2002 with a similar post-marketing commitment and a recommendation that Hoffman-La Roche and Schering Plough develop a joint pregnancy exposure registry for ribavirin to enroll from within the USA. In 2003, the Ribavirin Pregnancy Registry was established. In subsequent years, five additional ribavirin manufacturers joined the registry as their products were approved for use in the USA. The Ribavirin Pregnancy Registry (NCT00114712 [3]) is co-sponsored by the manufacturers of two brand products, Merck & Co. (formerly, Schering-Plough) and Genentech (a member of Hoffmann-La Roche), and five generic products from Aurobindo Pharma, Sandoz Inc., Teva Pharmaceuticals USA, Three Rivers Pharmaceuticals, and Zydus Pharmaceuticals USA.

### 1.2 Chronic Hepatitis C and Ribavirin

According to 2015 estimates, hepatitis C virus (HCV) affects approximately 1% of the world population, and 71 million are chronically infected [4]. Globally, an estimated

1.75 million new HCV infections occurred in 2015 resulting in a global incidence rate: 23.7 per 100,000 [4].

Based on a systematic review, the estimated number of US residents who have been infected with hepatitis C is at least 4.6 million (range 3.4–6.0 million) with 3.5 million (range 2.5–4.7 million) currently infected [5]. Incidence in the USA was decreasing until 2010, after which a doubling was reported between 2010 and 2014 [6]. Chronic HCV infection leads to liver disease in approximately 60–70% of infected individuals, 5–20% will develop cirrhosis over a period of 20–30 years, and 1–5% will die from hepatocellular cancer [7].

Ribavirin, with interferons and/or direct-acting antiviral medications, is used to treat chronic hepatitis C. Significant teratogenic effects have been demonstrated in all animal species exposed to ribavirin; therefore, ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant [1, 2]. The multiple-dose half-life of ribavirin is 12 days, and ribavirin may persist in non-plasma compartments for up to 6 months [8, 9]. Therefore, it is recommended that pregnancy be avoided not only during treatment, but also for 6 months following exposure [1, 2].

### 1.3 Animal Data

#### 1.3.1 Maternal Exposure

For maternal exposures, as described in the labeling, ribavirin produced significant embryocidal and/or teratogenic effects in all animal species in which adequate studies have been conducted and the female received the exposure directly [1, 2]. Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract have been reported [1, 2, 10–12]. Malformations occurred at doses as low as 1/20th of the recommended human dose of ribavirin [1, 2]. Teratogenic effects were observed at the lowest doses of ribavirin studied in rats and rabbits (0.3 mg/kg/day for both the rat and rabbit; approximately 0.06 times the recommended human 24-h dose of ribavirin). The incidence and severity of teratogenic effects increased with escalation of the drug dose. However, no maternal toxicity or effects on offspring were observed in a peri- and post-natal toxicity study in rats dosed orally at up to 1 mg/kg/day (estimated human equivalent dose of 0.17 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 0.01 times the maximum recommended human 24-h dose of ribavirin) [1, 2].

#### 1.3.2 Exposure through Male Sexual Contact

In studies of male rodents, ribavirin was associated with reversible germ cell toxicity, mutagenicity, and decreases

in epididymal sperm count [13–15]. Ribavirin also induced point mutations in germ cells, resulting in the formation of abnormal sperm [16]. However, it is suspected that sperm cell mutations may result in cell death [13], and morphologically abnormal sperm have been associated with infertility [17–19].

#### 1.4 Human Data

Data on human pregnancy exposures to ribavirin are limited. Single case reports and case series have been published that describe both normal pregnancies, resulting in healthy babies coincident with maternal and paternal exposure to ribavirin, and adverse pregnancy outcomes including spontaneous and induced abortions [20–25]. No birth defects have been reported except in the setting of concomitant teratogen exposure [24].

##### 1.4.1 Maternal Exposure

Maddrey [22] reported the pregnancy outcomes of ten women who took ribavirin during pregnancy; of these, four resulted in miscarriage, four were terminated, and two were lost to follow-up. Mishkin and Dechênes [20] described a woman directly exposed to ribavirin 3.5 months prior to conception, which resulted in a normal infant. Labarga et al. [25] reported a woman who was co-infected with HIV and HCV and received treatment with pegylated interferon, ribavirin, and antiretroviral therapy during the first 16 weeks of pregnancy. She delivered a healthy infant who, at 22 months of age, had no birth defects and no evidence of HCV or HIV infection. Valentin et al. [24] reported a live infant with trigonocephaly born to a woman with exposure to valproate and thyroxine throughout the entire pregnancy and ribavirin in early pregnancy (discontinued upon the diagnosis of pregnancy). Rezvani and Koren [26] report a normal pregnancy outcome following a systemic (injectable) first-trimester maternal exposure in a pregnant woman with severe acute respiratory syndrome (SARS).

##### 1.4.2 Exposure through Male Sexual Contact

Several case reports describe the outcomes of pregnancies with indirect ribavirin exposure (exposure occurring through the male sexual partner). From clinical trials, Maddrey [22] reported the outcomes of 15 pregnancies following prenatal ribavirin exposure through contact with a male sexual partner who had taken ribavirin. These pregnancies resulted in two healthy live born infants, four miscarriages, two terminations, and seven with unknown outcome. De Santis et al. [23] reported seven cases of peri-conception male exposures that resulted in six normal birth

outcomes and one spontaneous abortion. Hegenbarth et al. [21] reported two cases of male partner exposures occurring at 5 and 11 months prior to conception; both resulted in live born infants with no birth defects. Bianca and Ettore [27] report an indirect peri-conception exposure to ribavirin-interferon- $\alpha$ -2b with no adverse fetal effects.

The significance of indirect pregnancy exposures via the male sexual partner is unclear. Hofer et al. [28] measured ribavirin concentrations in blood and seminal fluid in 15 men with chronic HCV infections who were treated with pegylated interferon- $\alpha$ -2a in combination with ribavirin (Copegus<sup>®</sup>). Ribavirin concentration was two-fold higher in seminal fluid than serum levels. Semen abnormalities were common prior to treatment and increased during treatment.

Pecou et al. [29] evaluated a 37-year-old man exposed to ribavirin plus pegylated interferon for HCV infection and subsequent semen parameters and sperm DNA integrity. During treatment, he experienced a decrease in the percentage of progressive spermatozoa and the number of motile sperm per ejaculate. In addition, the round cell/spermatozoa ratio, suggestive of spermatogenic abnormality, increased from 2.6% ( $\pm$ 1.4%) to 23.6% ( $\pm$ 13.0%) during treatment but returned to baseline levels 4 months after treatment. The sperm DNA fragmentation index increased during treatment (from 14.5% before treatment to 69.2% at the end of 7 months of treatment) and remained elevated 8 months after treatment. The authors concluded that these alterations of spermatogenesis with DNA packaging abnormalities persisted 8 months after treatment and suggested that a longer pregnancy avoidance period after discontinuing treatment in men may be warranted.

#### 1.5 Study Aim

The registry's primary objective is to detect signals of any major teratogenic effect involving ribavirin exposure during pregnancy or within the 6-month period prior to conception in which exposure to ribavirin has incurred directly or indirectly. After 11 years of enrollment, the registry has reached the mid-point of its intended recruitment goal. This paper is an updated review of the background data and experience with a registry that began in 2003 and augments a prior review [30]. Data collected from registry inception on 23 December 2003 through 8 February 2016 were analyzed.

## 2 Methods

The Ribavirin Pregnancy Registry is an ongoing, voluntary, prospective, observational, exposure-registration cohort study conducted in the USA. The registry collects

information on both direct and indirect exposure to ribavirin during the 6 months prior to conception and throughout pregnancy. Direct exposure is defined as exposure occurring when a woman has received at least one dose of ribavirin during pregnancy or within the 6-month period prior to conception. Indirect exposure is defined as an exposure that occurs through sexual contact 6 months prior to pregnancy or during pregnancy with a man who is taking ribavirin or has taken ribavirin in the previous 6 months. For the purposes of defining exposure, the date of conception is defined as the first day of the last menstrual period (LMP).

The registry aims to enroll 158 live births following direct exposure and 158 live births following indirect exposure to ribavirin, providing 80% power to detect a relative risk of at least 2.6 in the overall number of birth defects reported to the registry compared to the overall rate as reported by the Metropolitan Atlanta Congenital Defects Program (MACDP). These sample sizes were based on the overall birth defect rate of 3.2% (6157/195,642) reported by MACDP at the time of registry initiation using a chi-square test and assuming a level of significance of  $p < 0.05$  [31]. An updated overall birth defect rate from MACDP of 2.67% was published in 2007 [32], and this rate, or a more recent update yet to be published, will be used in the final analysis when sample size requirements are met.

MACDP is a population-based birth defects surveillance system that is administered by the US Centers for Disease Control and Prevention (CDC). The primary objectives of MACDP are to monitor, regularly and systematically, births of malformed infants for changes in incidence or other unusual patterns suggesting environmental influences and to develop a case registry for use in epidemiological and genetic studies. MACDP actively searches for birth defects among the 50,000 annual births to residents of metropolitan Atlanta's five counties and abstracts medical records at all Atlanta obstetric hospitals, Atlanta pediatric referral hospitals, genetics labs, and vital records [31]. Birth defects from live births and fetal deaths, including induced abortions, are collected.

## 2.1 Enrollment

There are several ways in which a pregnant woman can be enrolled in the registry. The woman may initiate the enrollment process, or her healthcare provider may initiate enrollment on her behalf. When exposure occurs through male sexual contact, the man may initiate enrollment, and thereby allow medical record confirmation of his ribavirin dosing; after this, the woman may self-enroll or the healthcare provider may enroll her on her behalf. Manufacturers of ribavirin are alerted to pregnancy exposures primarily through reports from consumers and healthcare

providers. These reports are sent to the registry and included in the registry database.

To minimize the potential for biased ascertainment due to preferential reporting of abnormal outcomes, the registry encourages enrollment early in pregnancy before the outcome of pregnancy is known through prenatal diagnosis or the completion of pregnancy. Due to the high prevalence of prenatal testing in the USA, it is not feasible to exclude all women who have had prenatal testing [33]. Therefore, pregnant women may enroll in the registry as prospective participants if prior prenatal diagnoses do not include evidence of birth defects [33]. Women with abnormal prenatal tests before enrollment may participate in the registry, but their data are evaluated separately as retrospective reports. Although early reporting is preferred, enrollment may occur anytime during pregnancy.

## 2.2 Data Collection

Healthcare providers contributing data to the registry are typically prescribers of ribavirin (e.g., hepatologists), obstetricians, and pediatricians. Healthcare providers from each of these specialties may be contacted for each woman to collect information related to ribavirin, pregnancy, and the health of the infant, respectively. Participation in the registry does not require specific office visits or interventions. To minimize reporter burden and facilitate reporting, all registry data collection forms are brief, and may be submitted to the registry through a variety of reporting options (i.e., telephone, fax, mail, e-mail). Clinical data, particularly data related to pregnancy exposures and outcome, provided by the woman or male sexual partner, must be confirmed by their healthcare providers.

Enrollment and follow-up data are focused on ribavirin exposure, family history of birth defects, maternal risk factors and other potential confounders, pregnancy outcome including the presence or absence of birth defects, and newborn and infant health indicators. Maternal follow-up information is obtained during pregnancy and around the time of pregnancy outcome. Infant follow-up data is collected at birth and at 6 months and 1 year of age.

## 2.3 Follow-Up

The outcome of each pregnancy is classified into one of the following categories: live birth, miscarriage (defined as pregnancy loss occurring before 20 weeks of gestation), induced abortion, or stillbirth (defined as pregnancy loss occurring at 20 weeks or more of gestation). Gestational age is calculated from the first day of the LMP, or the estimated date of delivery (EDD) if LMP is not available. If a corrected EDD, generally by ultrasound, is available, it will be used for gestational week calculations over LMP

and EDD. The first trimester begins on the first day of the LMP, the second trimester begins at week 14, and the third trimester begins at week 28. The first day of the LMP is designated as the first day of pregnancy for estimations of exposure and gestational age.

## 2.4 Scientific Advisory Board Oversight

The registry's Scientific Advisory Board reviews all reports of birth defects among enrolled participants. Board members are listed on the registry's website [34]. The registry's Birth Defect Evaluator, a designated board member experienced in the identification and classification of birth defects, conducts an initial expert review, requests further information (as necessary), and provides an assessment of the relationship between the exposure and the outcome. The Birth Defect Evaluator assesses the available information for each birth defect and assigns an organ system classification [35] and MACDP classification [36]. The organ system classification facilitates the process of detecting a potential signal by grouping similar defects or defects with similar etiology together [35]. The MACDP coding improves comparability between the registry and the MACDP, and standardizes naming conventions for signal detection purposes. Annually, the Board reviews all new reports of birth defects based on the Evaluator's assessment and reaches a consensus on the final determination of the probable or possible association between the timing of the ribavirin exposure and development of the birth defect.

## 2.5 Analysis Methods

To maintain as much consistency with the MADCP birth defect surveillance system as possible without missing a potential signal, the registry defines birth defects as any major structural malformation or chromosomal abnormality diagnosed or with signs/symptoms before 6 years of age [31]. In addition, the definition of birth defects may include, on a case-by-case basis, and subject to independent review (1) any cluster of two or more conditional abnormalities or (2) any structural or chromosomal defect detected in the prenatal evaluation of a pregnancy or in the gross or pathologic examination of an abortus or deceased infant. The registry excludes birth defects attributed to prematurity (e.g., patent ductus arteriosus, patent foramen ovale, inguinal hernia) in the case definition [31].

The primary analysis population includes prospectively enrolled women from within the USA with all of the following attributes: (1) direct or indirect ribavirin exposure during pregnancy or the 6 months prior to pregnancy; (2) healthcare provider-confirmed exposure and outcome information; and (3) complete follow-up information on

pregnancy outcome through the end of pregnancy. Due to the greater potential for bias, subjects reported retrospectively after the outcome of the pregnancy is known and clinical study subjects are excluded from the primary analysis population. Analyses are stratified by direct or indirect ribavirin exposure and, in addition, by period of earliest exposure (i.e., within 6 months prior to conception; first, second, or third trimester).

Given the registry's voluntary, observational, and population-based characteristics, inclusion in the analysis population requires complete, healthcare provider-confirmed data on a limited set of variables (e.g., ribavirin exposure, pregnancy outcome, and birth defect status at the end of pregnancy). This streamlined data collection approach reduces reporter burden, which facilitates data collection and, thereby, increases the potential for signal detection. However, due to missing data, this approach often limits the ability to assess temporality and adequately describe the reported birth defects.

The birth defect rate was calculated by dividing the number of live born or stillborn infants (greater than 20 gestation weeks) with birth defects plus the number of induced abortions with birth defects by the number of live births within each exposure category. Using available data, preliminary birth defect rates and 95% confidence intervals (CIs) were calculated. The analysis was conducted with SAS<sup>®</sup> version 9.3 (SAS Institute, Cary, NC, USA).

## 3 Results

From 23 December 2003 through 8 February 2016, 464 exposed pregnancies have been prospectively reported (Table 1; Fig. 1). Due primarily to a loss to follow-up rate of 35.8% (166/464), only 58.6% (272/464) of these women met the conditions for the primary analysis population. Results presented here are based on the 272 women in the primary analysis population and the resulting 273 outcomes. Of the 272 pregnant women, 133 (48.9%) had direct exposures and 139 (51.1%) had indirect exposures (Table 1).

### 3.1 Maternal Characteristics

The demographics of the analysis population are presented in Table 2. The mean age of participating women at the time of enrollment was 29.7 years, with little difference between women with direct and indirect exposures. Self-reported race and ethnicity were distributed as follows: white 58.8% (160/272); Hispanic 8.8% (24/272); black 7.4% (20/272); other 3.7% (10/272); Asian 2.2% (6/272); and race not reported 19.1% (52/272). The variables representing age, clinical conditions, and race/ethnicity had

**Table 1** Valid prospective registry cases enrolled through 8 February 2016

	Ribavirin exposure source		Overall
	Direct <sup>a</sup>	Indirect <sup>b</sup>	
All valid prospective pregnant women enrolled	216	248	464
Pending cases <sup>c</sup>	2/216 (0.9%)	2/248 (0.8%)	4/464 (0.9%)
Cases lost to follow-up <sup>d</sup>	70/216 (32.4%)	96/248 (38.7%)	166/464 (35.8%)
Cases with an outcome	144/216 (66.7%)	150/248 (60.5%)	294/464 (63.4%)
All valid prospective cases with outcome	144	150	294
Analysis population <sup>e</sup>	133/144 (92.4%)	139/150 (92.7%)	272/294 (92.5%)
Patient reports, not medically confirmed <sup>f</sup>	4/144 (2.8%)	9/150 (6.0%)	13/294 (4.4%)
Medically confirmed non-US and/or clinical study reports <sup>g</sup>	7/144 (4.9%)	2/150 (1.3%)	9/294 (3.1%)

<sup>a</sup> Prenatal ribavirin exposure through the pregnant female who took ribavirin

<sup>b</sup> Prenatal ribavirin exposure through the pregnant female's male sexual partner

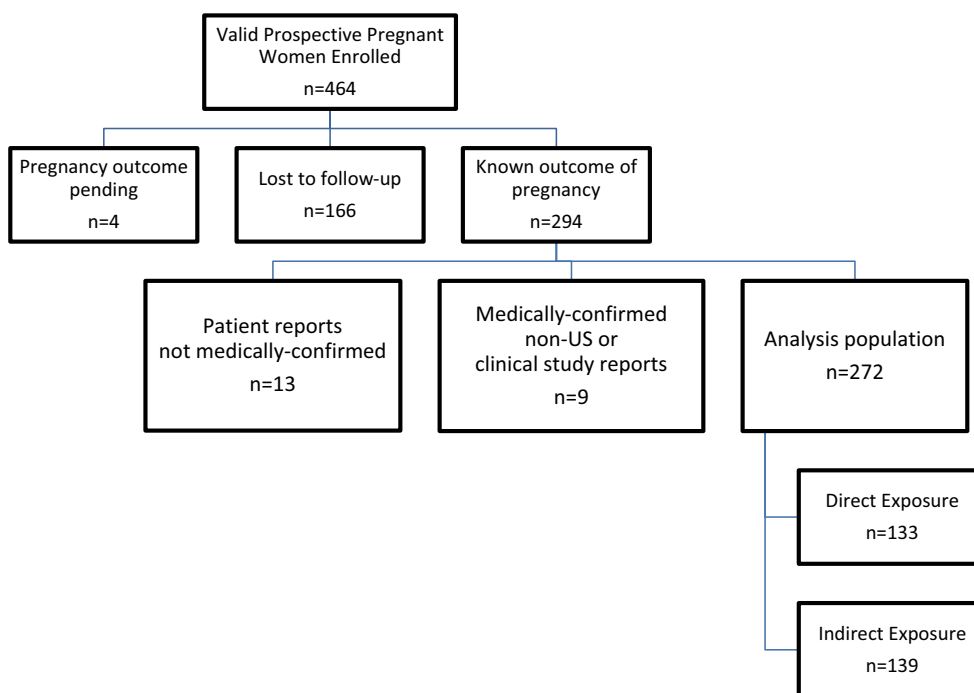
<sup>c</sup> Cases where the outcome of pregnancy is not yet known

<sup>d</sup> Outcome of pregnancy was not received despite multiple requests or if the reporter did not know if there was a birth defect

<sup>e</sup> Valid prospective US reports with a medically confirmed outcome reported (excluding clinical study cases)

<sup>f</sup> Valid prospective patient reports that have not been medically confirmed

<sup>g</sup> Valid prospective reports with medical confirmation from clinical studies or from non-US sources

**Fig. 1** Overall registry enrollment from 23 December 2003 through 8 February 2016 (includes direct and indirect exposures)

considerably more missing values among the indirectly exposed women than directly exposed women.

Hepatitis C infection was reported for nearly all directly exposed women (97.7%; 130/133) and only three (2.2%; 3/139) of the indirectly exposed women. At the time of this analysis, only one woman had reportedly received triple therapy during pregnancy, which included

the direct-acting antiviral medication telaprevir (Table 2). Prenatal testing prior to enrollment was reported for 25.4% (69/272) of the women in the analysis population (Table 2). Ten (3.7%; 10/272) women had prenatal testing for which the timing was unknown (pre- or post-enrollment); however, no birth defects were reported (Table 2).

**Table 2** Maternal demographics at enrollment in the analysis population: 23 December 2003 through 8 February 2016

	Ribavirin exposure type		Overall
	Direct <sup>a</sup>	Indirect <sup>b</sup>	
Pregnant women enrolled	133	139	272
Age at enrollment (years)			
<i>N</i>	123	110	233
Mean (SD)	29.3 (6.27)	30.1 (6.30)	29.7 (6.28)
Median (interquartile range)	28.0 (24.0–34.0)	30.0 (25.0–35.0)	29.0 (24.0–35.0)
Minimum, maximum	19–42	18–47	18–47
Missing	10	29	39
Age category (years) [ <i>n</i> (%)]			
18–29	67 (50.4)	53 (38.1)	120 (44.1)
30–39	47 (35.3)	51 (36.7)	98 (36.0)
40–49	9 (6.8)	6 (4.3)	15 (5.5)
Missing	10 (7.5)	29 (20.9)	39 (14.3)
Race/ethnicity [ <i>n</i> (%)]			
White	84 (63.2%)	76 (54.7)	160 (58.8)
Black	10 (7.5%)	10 (7.2)	20 (7.4)
Hispanic	12 (9.0%)	12 (8.6)	24 (8.8)
Asian	3 (2.3%)	3 (2.2)	6 (2.2)
Other	5 (3.8%)	5 (3.6)	10 (3.7)
Missing	19 (14.3%)	33 (23.7)	52 (19.1)
Prenatal testing [ <i>n</i> (%)]			
Yes, prior to enrollment	38 (28.6)	31 (22.3)	69 (25.4)
Yes, after enrollment	46 (34.6)	56 (40.3)	102 (37.5)
Yes, timing unknown	4 (3.0)	6 (4.3)	10 (3.7)
No	24 (18.0)	15 (10.8)	39 (14.3)
Unknown	11 (8.3)	6 (4.3)	17 (6.3)
Missing	10 (7.5)	25 (18.0)	35 (12.9)
Clinical conditions [ <i>n</i> (%)]			
Hepatitis C	130 (97.7)	3 (2.2)	133 (48.9)
HIV	0	0	0
Neither	3 (2.3)	96 (69.1)	99 (36.4)
Missing	0	40 (28.8)	40 (14.7)
Dual therapy <sup>c</sup>	132 (99.2)	139 (100.0)	271 (99.6)
Triple therapy <sup>d</sup>	1 (0.8)	0	1 (0.4)

SD standard deviation

<sup>a</sup> Prenatal ribavirin exposure through the pregnant female who took ribavirin

<sup>b</sup> Prenatal ribavirin exposure through the pregnant female's male sexual partner

<sup>c</sup> Dual therapy is the standard therapy of receiving interferon in combination with ribavirin

<sup>d</sup> Triple therapy is defined as receiving interferon, ribavirin, and an additional direct-acting antiviral drug such as boceprevir, telaprevir, sofosbuvir, or simeprevir

Among the 272 women in the primary analysis population, ribavirin exposure, categorized as the period of earliest exposure, occurred during the 6 months prior to conception for 88.6% (241/272) and during the first trimester for 10.7% (29/272) (Table 3). Two (0.7%; 2/272) women were exposed during the second trimester, and both were indirect exposures. There were no third trimester exposures reported.

### 3.2 Pregnancy Outcomes

Among the 272 pregnancies enrolled, there were 273 individual pregnancy outcomes (i.e., fetuses or infants), including one set of live-born twins who were exposed to ribavirin directly (Table 3). Among these 273 pregnancy outcomes, 66.0% (180/273) were live-born infants, 15.0%

**Table 3** Summary of pregnancy outcomes by trimester of earliest exposure—in the analysis population—23 December 2003 through 8 February 2016

	Prior to conception	First trimester	Second trimester	Third trimester	Overall
Pregnant women enrolled	241	29	2	0	272
Pregnancy outcomes <sup>a</sup>	242	29	2	0	273
Direct exposures	118/242 (48.8%)	16/29 (55.2%)	0/2	0/0	134/273 (49.1%)
Live birth	78/118 (66.1%)	7/16 (43.8%)	0/0	0/0	85/134 (63.4%)
Miscarriage <sup>b</sup>	17/118 (14.4%)	6/16 (37.5%)	0/0	0/0	23/134 (17.2%)
Induced abortion	23/118 (19.5%)	3/16 (18.8%)	0/0	0/0	26/134 (19.4%)
Stillbirth <sup>c</sup>	0/118	0/16	0/0	0/0	0/134
Indirect exposures	124/242 (51.2%)	13/29 (44.8%)	2/2 (100.0%)	0/0	139/273 (50.9%)
Live birth	84/124 (67.7%)	9/13 (69.2%)	2/2 (100.0%)	0/0	95/139 (68.3%)
Miscarriage <sup>b</sup>	14/124 (11.3%)	4/13 (30.8%)	0/2	0/0	18/139 (12.9%)
Induced abortion	25/124 (20.2%)	0/13	0/2	0/0	25/139 (18.0%)
Stillbirth <sup>c</sup>	1/124 (0.8%)	0/13	0/2	0/0	1/139 (0.7%)

<sup>a</sup> Includes multiple-birth outcomes. To date, there is one multiple-birth outcome (one set of live-born twin infants)

<sup>b</sup> Pregnancy loss occurring at <20 weeks of gestation

<sup>c</sup> Pregnancy loss occurring at ≥20 weeks of gestation

(41/273) were miscarriages, 18.7% (51/273) were induced abortions, and 0.4% (1/273) was a stillbirth.

There were slightly more live-born infants among the indirectly exposed outcomes (68.3%; 95/139) than directly exposed outcomes (63.4%; 85/134) (Table 3). The proportion of miscarriages among 134 directly exposed pregnancy outcomes was 17.2% (23/134) compared with 12.9% (18/139) among indirectly exposed outcomes. Although based on small numbers, miscarriages were considerably more frequent among first-trimester exposures than in women exposed prior to conception (Table 3).

Among the 51 women who had an induced abortion, 49.0% (25/51) indicated that ‘exposure to ribavirin’ or ‘potential for birth defects’ was an influential factor; 19.6% (10/51) cited reasons unrelated to ribavirin and 31.4% (16/51) did not provide a reason. Therefore, among the 35 women providing a reason for induced abortions, 25 (71.4%) indicated that exposure to ribavirin was a contributing factor. There were no reported birth defects among the 51 induced abortions; however, this information was unknown or missing for most (43/51; 84.3%) of these.

Of the 180 live-born infants in the primary analysis population, 45.6% (82/180) had follow-up data for both the 6-month and 1-year assessments, and 42.2% (76/180) did not have follow-up data for either. For infants without 6-month or 1-year pediatric follow-up data, the presence or absence of birth defects is determined using data collected at the time of birth only, often reported by the obstetrician. The primary reason for lack of follow-up data is inability to identify or engage the infant’s healthcare provider.

### 3.3 Birth Defects

The registry has received reports of 11 outcomes with birth defects in the primary analysis population, and all were among live-born infants (Table 4). Of the 85 directly exposed infants, seven had one or more reported birth defects [7/85 (8.2%) (95% CI 3.4–16.2)]. Of the 95 indirectly exposed infants, four had one or more reported birth defects [4/95 (4.2%) (95% CI 1.2–10.4)]. Of the 11 infants with birth defects, nine had structural defects. Two of the 11 infants had chromosomal/genetic diseases, which are unlikely to be related to ribavirin exposure. Patterns suggestive of a common etiology were not seen (Table 4).

### 3.4 Losses to Follow-Up

Among the 464 women enrolled in the registry, 35.8% (166/464) were lost to follow-up (Table 1), of whom 77.1% (128/166) had medically confirmed enrollment criteria and 22.9% (38/166) did not.

Women who self-enrolled had the lowest rate of loss to follow-up (15.7%; 24/153), followed by women who were initially reported by a healthcare provider (26.5%; 45/166). Women who were reported to the registry through the manufacturers’ pharmacovigilance networks had the highest rate of lost to follow-up (72.8%; 59/81). These rates were based on the combined group ( $n = 400$ ) of women in the analysis population ( $n = 272$ ) plus those who were lost to follow-up with medical confirmation of enrollment criteria ( $n = 128$ ).



**Table 4** Reported birth defects following direct or indirect ribavirin exposure, by earliest exposure to ribavirin

Case no.	Exposure window	Ribavirin exposure details (as available)	Reported abnormalities/sex of infant	Additional information
<b>Direct exposure</b>				
1	Prior to conception	Approximately 4 months prior to LMP	Cardiac VSD and cyst of 4th ventricle of brain/sex missing	Ribavirin prescriber reported defects. The registry was unable to obtain confirmation or additional information from the infant's pediatrician. No information was provided on medication exposures or concurrent medical conditions during pregnancy
2	Prior to conception	During the 2–3 months prior to LMP	G6PD deficiency/female	Tobacco use was reported in the preconception period and the 1st trimester. G6PD deficiency is a genetic disorder; ribavirin exposure may be irrelevant
3	Prior to conception	Approximately 3 months prior to LMP	Hearing loss/male	No birth defects or reports of hearing loss were received from 6-month and 1-year pediatric follow-up. The registry completed follow-up and considered the case closed. The registry was contacted when the infant was 19 months old with a report of 80% hearing loss, unconfirmed by a healthcare provider. The registry was unable to confirm hearing loss or obtain additional information from the infant's pediatrician regarding the diagnosis and current health status
4	Prior to conception	Exposure ended approximately 3 months prior to LMP	Deafness/male	Deafness reported at birth by obstetrician. The infant failed a hearing test at birth and failed the ABR screening test at 6 months. Maternal medication use prior to and during pregnancy included atazanavir, ritonavir, emtricitabine/tenofovir, and albuterol inhaler. The mother reportedly smoked tobacco prior to pregnancy and during the 1st and 2nd trimesters
5	Prior to conception	Exposed until approximately 1 month prior to LMP	Secundum ASD with left to right shunt/female	Diagnosed at 5 days of age. The registry was unable to obtain additional information on severity. At 7 months, a transthoracic echocardiogram indicated that the secundum ASD had resolved, and no additional cardiac abnormalities were found. Maternal medication use during pregnancy included albuterol for asthma
6	Prior to conception and 1st trimester	Began approximately 5 months prior to LMP and continued until approximately 3 weeks of gestation	Torticollis/female	Born at 33.4 weeks of gestation. Torticollis noted at the 6-month and 1-year pediatric assessments, which resolved temporarily around 6 months of age. Other pregnancy exposures included treatment for type 1 diabetes: insulin, Humalog <sup>®</sup> , and Humulin <sup>®</sup> . Tobacco use through second trimester
7	1st trimester	Exposed for 1 day around the 4th week of gestation	Hypospadias—dorsal penile hood with incomplete foreskin and penile chordee/male	Intrauterine growth restriction was diagnosed by ultrasound at 34.1 weeks of gestation and at 37.1 weeks. Maternal medical history included hyperthyroidism in the 2nd trimester that was treated with propylthiouracil, and hypothyroidism in the 3rd trimester with no treatments specified. The woman also had sickle cell trait and a history of GERD that began prior to conception. Other medication exposures included the Tdap vaccine in the 3rd trimester

Table 4 continued

Case no.	Exposure window	Ribavirin exposure details (as available)	Reported abnormalities/sex of infant	Additional information
Indirect exposure				
8	Prior to conception until around the time of conception	Approximately 3 months prior to LMP until conception, reportedly with no unprotected intercourse during pregnancy	Hypospadias/male	Paternal history of hypospadias. The woman developed high blood pressure early in pregnancy and reportedly had a diagnosis of anxiety prior to conception. Concurrent medications for these conditions were not reported
9	Prior to conception until around the time of conception	Approximately 6 months prior to LMP; ongoing around the time of conception	Torticollis (absent/hypoplastic sternocleidomastoid muscle)/female	Family history of birth defects is significant for an unknown type of neurological disease in offspring of maternal cousin and nephew. The mother's medical history included chronic back pain, hypothyroidism, depression, high cholesterol, allergies, anxiety, and hypertension. She was taking multiple medications during pregnancy (levothyroxine, oxcarbazepine, loratadine, hydrocodone, clonazepam, bupropion, diazepam, ramipril, olmesartan medoxomil-hydrochlorothiazide, potassium supplements, furosemide, and atenolol). Multiple prenatal tests were conducted throughout the pregnancy, and birth defects were not detected
10	Prior to conception and 1st trimester	Prior to LMP and during the 1st trimester (unprotected intercourse multiple times per week ending around the 12th week of pregnancy)	Down syndrome/trisomy 21/male	The mother was 42 years old at conception. No medication exposures or concurrent medical conditions were reported. The woman smoked tobacco prior to conception and throughout pregnancy. Down syndrome is a chromosomal disorder; ribavirin exposure may be irrelevant
11	1st trimester	Exposed during 1st trimester	Polydactyly (post-axial, right foot) and neonatal tooth/female	Family history of both anomalies: polydactyly (maternal grandfather), neonatal tooth (father). Mother is Hispanic (race not specified) and is an insulin-dependent diabetic who reportedly takes insulin as needed. Information on glucose control was not provided. Maternal medication exposures during pregnancy include insulin, acetaminophen, and prenatal vitamins. In addition to diabetes, idiopathic thrombocytopenic purpura and gastroenteritis during pregnancy were reported

*ABR* auditory brainstem response, *ASD* atrial septal defect, *G6PD* glucose-6-phosphate dehydrogenase, *GERD* gastroesophageal reflux disease, *LMP* first day of last menstrual period, *Tdap* tetanus, diphtheria, and pertussis, *VSD* ventricular septal defect

## 4 Discussion

The Ribavirin Pregnancy Registry was designed to evaluate the potential human teratogenicity of prenatal exposure to ribavirin. After more than 12 years, the registry has reached the mid-point of enrollment. Eleven outcomes with birth defects have been reported, and all were among live-born infants (Table 4). Nine of the 11 infants had structural defects: two infants with torticollis; two infants with hypospadias; two infants with hearing-related conditions (deafness and 80% hearing loss); one infant with polydactyly (post-axial, right foot) and a neonatal tooth; one infant with both a ventricular septal defect and a cyst of the fourth ventricle of the brain; and one infant with atrial septal defect (ASD). Two of the 11 infants had genetic conditions: one with glucose-6-phosphate dehydrogenase deficiency and one with Down syndrome.

To be conservative and avoid missing a potential signal, the registry counts all 11 infants with birth defects as cases in the calculation of the direct and indirect birth defect rates (Table 4). However, for several of the 11 infants, an alternate origin may be etiologic. Two of the 11 infants with birth defects had chromosomal/genetic disorders (Table 4, Case Numbers 2 and 10); therefore, it is unlikely that these conditions were related to ribavirin. Among the structural defects, two infants had a family history of the same defect, suggesting an inherited cause or predisposition. One of the infants with hypospadias had a paternal history of hypospadias (Table 4, Case Number 8), and the infant with polydactyly (post-axial, right foot) and a neonatal tooth had a family history of both defects (Table 4, Case Number 11). Of the two infants with torticollis (Table 4, Case Numbers 6 and 9), one was reported as intermittent and, therefore, may be attributed to positioning in utero (Table 4, Case Number 6) [37]. For the infant with 80% hearing loss (Table 4, Case Number 3), there was no mention of this condition during the routine 1-year follow-up. This abnormality was first reported to the registry when the infant was 19 months of age, after participation in the registry was completed. The hearing loss was reported by the mother and was not confirmed by a healthcare provider. Hearing loss with a delayed onset is not characteristic of congenital deafness and suggests other prenatal factors (e.g., genetic diseases, congenital cytomegalovirus infection) or post-natal environmental factors, although none were reported. Finally, regarding the infant with secundum ASD (Table 4, Case Number 5), the report was based on auscultation of a murmur at birth, and the registry was unable to obtain information on severity. However, the registry learned that at 7 months of age, the infant had a transthoracic echocardiogram, which indicated that the secundum ASD had resolved, and no additional

cardiac abnormalities were found. The infant was included in the birth defect rate as a case, because the defect was present at birth, which is consistent with the handling of cases in the comparator population from MACDP [31]. The registry reports a variety of conditions among the 11 birth defect cases but has not detected patterns among subjects or similarities to the animal data [2, 10–12] suggestive of a teratogenic mechanism.

The strength of evidence surrounding the association between ribavirin and human birth defects is weak. The birth defect rates should be interpreted cautiously, as several of the birth defects currently included in the direct exposure birth defect rate of 8.2% (7/85; 95% CI 3.4–16.2) and the indirect exposure rate of 4.2% (4/95; 95% CI 1.2–10.4) may be unrelated to exposure. The MACDP birth defect rate of 2.67% is within the CIs for indirect exposures but not for direct exposures [32]. However, the large variance in both estimates indicates that calculation of relative risk is premature and unreliable. Given that current enrollment is far short of the desired number based on sample size calculations, the ability to estimate risk and reach conclusions about direct or indirect exposures is limited.

Regarding the embryocidal activity reported in animal studies [1, 2], the registry reports one stillbirth and an overall miscarriage rate of 15.0% (41/273) that is consistent with estimates of miscarriage the US general population [38]. Examining the miscarriage rate by trimester of earliest exposure indicates a considerably higher rate of miscarriage among women following first trimester exposure in the direct (37.5%; 6/16) and indirect (30.8%; 4/13) exposure groups. The significance of these findings is difficult to assess given the small number of women in these strata and the limitations in the study design for capturing early miscarriages. As ribavirin is used in combination with interferon- $\alpha$  for the treatment of chronic hepatitis C infection, it is relevant to note that interferon- $\alpha$  has been shown in preclinical animal studies to have abortifacient properties [1, 2].

The pace of enrollment in this registry has been slower than expected, and this is likely the result of two factors, which reduce the potential for pregnancy exposures: the introduction of new direct-acting, ribavirin-free, antiviral medication regimens for hepatitis C and risk-minimization activities emphasizing pregnancy avoidance associated with ribavirin. Risk-minimization activities for ribavirin include the FDA Pregnancy Category X designation; the boxed warning in the prescribing information regarding pregnancy avoidance; and a warning in the medication guide about the need to avoid pregnancy, which is emphasized and prominently placed in the document. If these activities have been effective, the availability of

exposed pregnancies is expected to decrease as consumers become more aware of the importance of pregnancy avoidance while taking ribavirin and during the 6 months after ribavirin has been stopped.

Approximately 20% of registry participants chose induced abortions for their ribavirin-exposed pregnancies. While this rate is consistent with overall general population estimates in the USA [39], the registry rate and the general population rate describe two distinctly different populations. The registry's induced abortion rate may be an underestimate among all ribavirin-exposed pregnant women as it represents only the population of women deciding to enroll in the registry and terminate the pregnancy thereafter. The registry is unable to quantify the number of women choosing to terminate the pregnancy prior to interacting with the registry. Of concern is the 71.4% (25/35) of enrolled women choosing induced abortion due to a fear of birth defects related to ribavirin exposure. This underscores the importance of completing enrollment in this registry so that informed decisions can be made about the safety of ribavirin exposure during pregnancy.

Over one-half of the pregnant women comprising the analysis population were indirectly exposed. Many questions remain about the safety of indirect pregnancy exposure to ribavirin, particularly whether ribavirin contained in seminal fluid will exert deleterious effects on sperm and fertilization of the ova. Scientific evidence supports ribavirin as genotoxic to sperm cells in mice and rats. In humans, the genotoxicity data are based on peripheral blood smears and not in human sperm cells [40]. Studies in human subjects have shown that concentrations of ribavirin in the seminal fluid may be higher than initially expected [28, 29].

Given the observational design and voluntary nature of this registry, missing data, and, at times, a lack of critical details necessary to optimally characterize birth defects and their association with ribavirin are limitations to this study. Missing data on family history of birth defects is problematic, as a birth defect may appear to be temporality related to ribavirin exposure when the most likely reason for the birth defect is genetic. Some birth defects may go unreported due to incomplete infant follow-up data; for example, some neurosensory or cardiac defects may not be observed by 1 year of age. Also, if the registry was unable to engage the pediatrician, birth defects that are typically identified later in infancy, which would have been captured in the 6-month or 1-year follow-up, may be underreported. Over-estimating the birth defect rate may have occurred due to the conservative approach used by the registry whose assessors are not blinded to the exposure when classifying birth defects. To avoid missing a potential signal, the registry classifies infants with birth defects as

cases in the calculation of the direct and indirect birth defect rates when there may be a clear association with a genetic or environmental factor. In addition, the registry has a high lost to follow-up rate, which varies by the type of initial reporter (i.e., patient, healthcare provider, registry sponsor), and this limits the precision of estimated rates and the power of the comparison to MACDP.

The availability of an appropriate disease-specific comparison group, such as a population of pregnant women with HCV infection but not exposed to ribavirin during pregnancy, poses a considerable challenge to the estimation of relative risk. On an ongoing basis, the Ribavirin Pregnancy Registry researches the medical and pediatric literature to obtain appropriate background rates should they become available. To date, the registry has not been successful in identifying pregnancy outcome data for a comparison group of women with HCV who have not taken ribavirin during the registry's exposure window.

The methods used in the Ribavirin Pregnancy Registry differ considerably from the CDC MACDP, and this is a limitation to the validity of this study design. MACDP is a population-based, active surveillance system based on birth defect ascertainment from retrospective record review in the metropolitan Atlanta, Georgia area. In contrast, the registry is a voluntary, prospective study, which enrolls reported pregnancies and actively solicits pregnancy outcomes, from anywhere in the USA. MACDP collects data from live-born infants and fetuses 20 weeks of age or older (including pregnancy outcome data from induced abortions), whereas the registry collects data on birth outcomes of any gestational age. Given these limitations, comparisons with MACDP must be interpreted with caution.

Connell et al. [41] conducted a retrospective cohort study of all Florida births from 1998 to 2007 using birth certificate records linked to hospital discharge data and found that women with hepatitis C infection were more likely to have infants with congenital anomalies (odds ratio 1.55; 95% CI 1.14–2.11). The variable representing congenital anomalies was a composite of all congenital anomalies reported in the secondary databases used in this study, and maternal medication use was not evaluated. The cohort dates (1998–2007) are prior to the introduction of direct-acting antiviral agents for HCV in the USA in 2011. Therefore, it appears that prenatal ribavirin exposure during pregnancy cannot be ruled out in this population and, thus, this cohort may not be an unexposed population. Connell et al. [41] reported that 4.6% of 988 women with hepatitis C had infants with congenital anomalies. This rate is higher than the MACDP rate of 2.67% [32] and falls between the Ribavirin Pregnancy Registry rates of 8.2% for direct exposures and 4.2% for indirect exposures.

## 5 Conclusion

Based on the patterns of birth defects reported, preliminary findings do not suggest a clear signal of human teratogenicity for ribavirin; however, the current sample size is insufficient for reaching definitive conclusions. When this study was initiated, ribavirin was a relatively new medication with limited data on its use, particularly among pregnant women. Since that time, both the availability of secondary data for research (e.g., claims data, electronic health records data) and experience with ribavirin has increased. A study of this topic using a large secondary database that includes medication exposure may provide more data than a voluntary registry; however, this was not a feasible option in 2003. Nonetheless, secondary data on ribavirin use could provide an estimate of the extent of ribavirin use in the target population and thereby improve enrollment projections.

Completion of this registry's enrollment and dissemination of its findings to inform practice will continue to be delayed until the registry meets its sample size goals. Despite a diminishing population from which to enroll exposed pregnancies, pregnancy exposures continue to occur, and the registry will continue to enroll both direct and indirect pregnancy exposures to ribavirin and optimize awareness activities. Healthcare providers are encouraged to report exposed pregnancies to the registry. Additional information is available at [www.RibavirinPregnancyRegistry.com](http://www.RibavirinPregnancyRegistry.com).

### Compliance with Ethical Standards

**Ethical approval and informed consent** The protocol for the Ribavirin Pregnancy Registry conforms to the ethical guidelines of the 1975 Declaration of Helsinki and is approved by Western IRB (WIRB). The Institutional Review Board (IRB) has waived documentation of informed consent in accordance with federal regulations [21 CFR 56.109(c)(1)], which allows the registry to verbally consent patients over the telephone [42]. The IRB has also approved a waiver of the informed consent process when a healthcare provider contacts the registry and provides registration and follow-up anonymously using a registry-assigned tracking number rather than personal identifiers.

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**Conflict of interest** Susan Sinclair serves as the principal investigator for the registry and is reimbursed for her time through INC Research. Judith K. Jones, Richard K. Miller, Paul Y. Kwo, and Willis C. Maddrey are members of the Scientific Advisory Board, reimbursed for their time by the sponsors, and have no conflicts of interest that are directly relevant to the content of this study. Michael F. Greene is an unpaid Scientific Advisory Board member and has no

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