Case report

Paternal exposure to ribavirin: pregnancy and neonatal outcome

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We report seven cases of newborns conceived within 6 months from the end or during paternal ribavirin exposure.

Introduction

Ribavirin is a nucleoside analogue associated to interferon-α in standard treatment of patients with chronic hepatitis C.

Due to teratogenic and mutagenic effects documented in preclinical studies, maternal or paternal ribavirin exposure, or both, is contraindicated before conceiving and during pregnancy. The manufacturer labels the drug as Food and Drug Administration risk factor category XM.

In pregnant animals teratogenic and embryo toxic risks were dose- and time-dependent [1–5]. Consequently, product labels advise at least a 6-month waiting period prior to gestation in childbearing women after the end of treatment [6].

Current literature reports nine cases of maternal ribavirin exposure during the second trimester and only one case during the first trimester: no fetal or neonatal effects were observed [7,8].

Ribavirin teratogenity is also supposed in case of paternal exposure. The drug accumulates in the sperm and causes alterations at lower doses than those proposed for humans [6].

Ribavirin effects were investigated on testicles and sperm in mice at 3–6 months. Spermatozoa alterations have been observed at doses of 15 mg/kg but complete recovery resulted within 1–2 cycles of spermatogenesis [2,6].

Based on these investigations and on a multiple dose half-life of ribavirin of 12 days (e.g., 15 half-lives of clearance for ribavirin), male patients are warned by the manufacturer to wait for a 6-month period before conception [6]. They are also advised to utilize barrier contraception so that risk of drug emission into the vagina is minimized, since it is unknown if ribavirin may exert hypothetical teratogenic effects by direct action on the sperm or by a significant absorption via female mucosa [6].

Actually, there are no epidemiological human studies about pregnancies post or through paternal ribavirin exposure and current knowledge is restricted to a few cases [8–10].

Seven pregnancies with paternal ribavirin exposure were referred to our Teratology Information Service (TIS) between March 2000 and August 2001. We have been prospectively following all the cases exposed to paternal ribavirin by telephone interviews during pregnancy and up to 14 months after delivery. At the end of the second trimester we interviewed all patients, asking them if the fetal development was normal. If there were doubts about congenital malformations, pregnant women were admitted to the Prenatal Diagnosis Service of our hospital where they underwent ultrasound exams. Then, after the expected date of delivery, we called patients to find out the obstetrical and neonatal outcome, and if congenital anomalies were documented. No babies needed to be visited by paediatricians skilled in birth defects, since their follow-ups were normal.

Case 1

A 35-year-old patient, V pregnancy, 4 para, hepatitis C virus (HCV)-negative, whose partner was HCV-positive, and treated with interferon and ribavirin (600 mg/day) for 1 year until 1 month before conception. Patient consulted us at 11 weeks of gestational age. She reported unprotected intercourse with partner throughout pregnancy. The patient did not undergo amniocentesis or any other invasive prenatal investigations. At 36 weeks she
delivered a normal male newborn, 2570 g, with APGAR 10/10. Baby's follow-up was normal at 14 months.

Case 2
A 29 year-old patient, first pregnancy, HCV-negative, with HCV-positive partner who was exposed to ribavirin (600 mg/day) and interferon between week 2 and 6 of gestational age. Patient referred unprotected intercourse through pregnancy. She underwent amniocentesis with normal fetal karyotype and delivered a healthy female at term (3350 g, APGAR 9/9). Regular follow-up was at 11 months.

Case 3
A 35 year-old patient, first pregnancy, HCV-negative, whose HCV-positive partner was treated with ribavirin (1000 mg/day) and interferon for 10 days, 3 months prior to conception (therapy was interrupted due to side effects). The patient consulted us at 8 weeks of gestational age and did not undergo amniocentesis. The couple had avoided intercourse during pregnancy. At term she delivered a male, without malformations, by caesarean section following obstetrical indication (3100 g, APGAR 9/10). Baby's follow-up was normal at 3 months.

Case 4
A 34 year-old patient, second pregnancy, 1 para, HCV-negative. At 9 weeks she consulted our Service because of her HCV positive partner's exposure to combined therapy with interferon and ribavirin (600 mg/day). It was ceased 2 months before conception. The patient did not undergo amniocentesis and the couple had unprotected intercourse through pregnancy. At 37 weeks a female was delivered, 2900 g, and APGAR 9/10. No evidence of neonatal anomalies; normal follow-up at 3 months.

Case 5
A 28 year-old patient, HCV-positive, whose partner (HCV-positive) underwent combined interferon and ribavirin therapy (600 mg/day) for 7 months. He gave up his treatment 1 month before conception. The patient had a very early miscarriage at 5 weeks.

Case 6
A 19 year-old patient, first pregnancy, HCV-negative. At 12 weeks of gestational age she called our TIS because of her HCV-positive partner’s exposure to ribavirin (1000 mg/day). Therapy was begun 11 months before conception and it was given up after consulting our service. Amniocentesis was not performed and we have no data about intercourse in pregnancy. She delivered twins by caesarean section following obstetrical indications at 36 weeks. Two healthy babies were born, 2600 g, respectively, and good APGAR scores. Both follow-ups were normal at 6 months.

Case 7
A 34 year-old patient, second pregnancy, 1 para, HCV-negative, consulted us at 8 weeks of gestation. Her HCV-positive partner was exposed to ribavirin (600 mg/day) and interferon for 7 months and he discontinued treatment 1 month before pregnancy. She had intercourse with prophylactics during gestation and did not undergo amniocentesis. A healthy baby of 3750 g (normal APGAR score) was delivered by vaginal delivery at 40 weeks.

Conclusions
Our experience reports seven cases of paternal exposure to ribavirin up 6 months prior to conception to 12 weeks of gestational age. Specifically, two cases underwent paternal exposure during conception (until 6 and 12 weeks of gestational age without barrier contraception, respectively). The other five cases gave up ribavirin treatment from 3 to 1 month before conceiving. Although six cases were also exposed to interferon (IFN-α-2b), it is not considered dangerous for the fetus. Interferon belongs to Class C according to the FDA; it is able to inhibit testicular function but does not cross the placenta [11,12].

These data demonstrate that pregnancy is not a rare occurrence during paternal exposure to ribavirin (seven cases in 17 months), despite the pharmaceutical company warnings. By contrast, during the same period, we only had one case of maternal exposure, lost at follow-up. We suppose that birth control is weaker during paternal than maternal exposure since there is not clear less evidence that it is teratogenic in the former case. In this case By consequence, couples do not consider legal abortion as are aware that pregnancy is almost completely unsafe after paternal exposure and they contact our TIS to get more information instead of terminating their gestation. This experience and lack of data relative to pregnancy following paternal ribavirin exposure, justify our effort to collect as cases as possible.

Our data refer no congenital anomalies and only one miscarriage (therapy was given up 1 month prior to conception). Seven healthy babies were born with no complications during pregnancy or during follow-up from 3 to 14 months post-delivery. Currently our study represents the only prospective investigation of paternal ribavirin exposure. Our seven cases increase previous data of literature (with complete follow-up) about paternal exposure.
Maddrey [9] reports 15 cases of paternal exposure to ribavirin but only two women delivered healthy babies since four of them had a miscarriage, two underwent legal abortions and seven failed to attend follow-ups.

Hegenbarth and Mishkin [8,10] refer two pregnancies during paternal drug intake: therapy was begun for 5 and 11 months before conceiving, respectively. No malformations were observed in either case.

In our experience, spontaneous abortion rate does not increase (1/8 vs 4/6 by Maddrey) [13] and neither of the newborns shows specific congenital malformations. Even if our data are limited, they are the most numerous group of babies conceived during or within 3 months after the end of paternal ribavirin exposure, compared to the current literature. The lack of literature data relative to pregnancy and neonatal outcome justify our ongoing effort to collect as many cases as possible.

During the counselling of couples whose pregnancy occurs although there has been paternal ribavirin exposure, it is important to look up all the known human cases since the drug is at the moment considered a potential teratogen. Consequently, we believe it suitable to warn couples that we are deficient in controlled studies and we still recommend performing an accurate fetal ultrasound examination at 19–24 weeks of gestational age.

Since controlled investigations are not possible (because of ethical reasons), a multicentric study should be available among teratogen information services. Data collection about cases of paternal or maternal ribavirin exposure, or both, is necessary in order to obtain significant statistics analysis.

References

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