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Case report

Pregnancy outcome after exposure to injectable ribavirin during embryogenesis

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Abstract

We describe normal pregnancy outcome in a case of first trimester exposure to injectable ribavirin in a 36-year-old pregnant woman who received three intramuscular injections of ribavirin for suspected SARS. She delivered at 40 weeks of gestation a healthy baby girl. In pediatric follow up at 8 month of age, physical examination and neurodevelopmental milestones were normal.

Keywords: Ribavirin; Pregnancy; First trimester

Ribavirin is a broad spectrum nucleoside analogue efficacious in the treatment of several viral infections, and commonly used in the treatment of respiratory syncytial virus (RSV) infection. Ribavirin exerts its antiviral effects by inhibiting inosine monophosphate dehydrogenase [1–3]. Inhibition of this enzyme prevents biosynthesis of guanine nucleotides and interferes with DNA and RNA replication. Because of its ability to obstruct the biosyntheses of guanine nucleotides, ribavirin treatment during pregnancy specifically in the first trimester may have the potential to interfere with embryonic development.

Ribavirin exhibits two stages of elimination with a relatively short plasma half-life (2 h), followed by a longer terminal half-life of 16–164 h. This is due to slow release of the active metabolite, ribavirin triphosphate, from erythrocytes [4]. In adults, an oral dose of 600 mg ribavirin yields peak plasma concentration of 1.3 mcg/mL with bioavailability of 40–50%. An intravenous dose of 1000 mg results in mean concentration of 24 mcg/mL, whereas the aerosolized preparation yields serum concentrations between 0.2 and 1 mcg/mL. In contrast, ribavirin levels in respiratory secretions can be 1000-fold higher and following secondary aerosolized drug exposure in health care workers, the inhaled systemic absorbed dose would be less than 0.1% of the oral therapeutic dose [5,6].

In the recent severe acute respiratory syndrome (SARS) outbreak, ribavirin was used in various countries against this novel coronavirus [5]. Initial reports noted improvement in surrogate markers of outcome, such as resolution of fever and improvement in oxygenation and radiographic appearance [7–9]. Ribavirin dose recommended for treatment of SARS was 400 mg intravenous (IV) every 8 h for 3 days, then 1200 mg orally twice daily for 7 days, although there were large variations in the dose regimens in different institutions [5].

Preclinical studies in pregnant rodents using doses within or below the human therapeutic range produced teratogenic effects that were dependent on both dose and time of exposure [2,10–12]. The frequency of skeletal malformations was increased significantly among the offspring of pregnant mice exposed to ribavirin in doses 1–10 times those used in humans [1]. While no malformations were seen among surviving offspring of rabbits when pregnant rabbits were treated orally with ribavirin in doses smaller than those used in human, there were increased rates of embryonic and fetal death [12]. In another study, treatment of seven pregnant baboons with doses three to six times larger than the human oral dose did

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not result in teratogenicity [12,2]. It is not known whether ribavirin can cause similar harm in humans.

The concerns regarding the potential teratogenicity for women of childbearing age with secondary exposure to aerosolized ribavirin have been studied (e.g. in nurses and mothers). Several investigators have collected blood and urine specimens from health care workers or volunteers exposed to aerosolized ribavirin to assess the potential exposure to environmental ribavirin. Three studies suggested that secondary absorption of ribavirin by health care workers, if it occurs, is minimal. Although no toxic or adverse effects of ribavirin aerosol were observed in the participants, perception of teratogenic risk and anxiety are often high [6,13,14].To date there have been no published reports related to ribavirin exposure during the first trimester of pregnancy. There is a report of nine pregnant women who were treated with ribavirin during the second half of pregnancy for severe measles infection. Eight women received therapy for 1–6 days via a facemask and one woman received therapy for 5 days via an endotracheal tube. All infants were healthy with no adverse effects [15]. During the community outbreak of SARS in Hong Kong, five live born infants were born to pregnant women with SARS receiving ribavirin in late pregnancy. All five mothers received (IV) ribavirin during the acute phase of their disease and subsequently two of the newborns received ribavirin IV as part of their management as well. Three mothers delivered their baby shortly after receiving ribavirin and two who had ribavirin at 27 and 30 weeks continued their pregnancy delivering healthy babies at 33 and 37 weeks [16].

1. Case report

A 36-year-old G2P0SA1 woman traveled to China during the SARS outbreak. At the time, she was not aware that she was 7 weeks pregnant and during her stay in China she developed cold and cough symptoms. She was seen by a physician who advised her to receive a total of six injections of 200 mg ribvirin intramuscularly (IM) daily for three days. Eventually she received a total of three injections of 200 mg IM ribavirin within a 3-day period. She did not recall receiving any other medications beside ribavirin. The possibility of SARS in her case was ruled out by further investigation, and her cold symptoms subsided. She continued her pregnancy without any complications and at 13 weeks of pregnancy she called Motherisk in order to get information regarding ribavirin exposure and possible adverse effects on her current pregnancy. She was sent for ultrasound (US) at 11, 18 and 27 weeks of pregnancy and all reported to be within the normal range. Because of her age, she underwent amniocentesis at 18 weeks of pregnancy with negative results. Her pregnancy continued uneventfully. She developed some contractions at 40 (+3) weeks and with the assist of induction she delivered a baby girl with normal Apgar scores. Birth weight was 3.35 kg (7 lb and 6 oz). Her baby did not need any specific medical attention and did very well during the hospital stay. She and her baby were discharged from the hospital at 48 h. Her newborn developed mild jaundice on postnatal day 3 which did not necessitate any treatment and subsided after a few days. According to maternal report, her baby is 8 months old and healthy. She stated that the child has been followed by a pediatrician since birth. She was last seen by her pediatrician at 8 months of age. As reported by the infant's pediatrician, her physical examination was completely normal with no evidence of malformations or minor anomalies. She was able to sit up straight by herself without any support, babble, and have central grasping at 8 months of age. Her pediatrician also confirmed that her neurodevelopmental milestones have been within the normal range. The mother did not express concerns regarding the growth and health of her baby at the time of the follow up interview.

2. Discussion

Severe acute respiratory syndrome is a highly infectious disease with high rates of morbidity and mortality. The major therapeutic modalities in its treatment have been empirical. Critically, affected pregnant women had to be treated with potentially teratogenic drugs. The most commonly used first-line medications during the outbreak were ribavirin and corticosteroids [5,8,9]. Ribavirin has an FDA pregnancy category *X*, indicating high teratogenic probability based on consistent animal studies and biological plausibility. Hence, the drug is contraindicated in women who are or may become pregnant. If the use of ribavirin is considered critical by the physician, the pregnant patient should be made aware of the potential teratogenic effects of ribavirin and the limited information on its use in human pregnancy. While concerns of teratogenicity are higher in the first trimester during organogenesis, ribavirin may theoretically also cause functional defect even after the first trimester [17]. The manufacturer (Schering Corp. http://www.ribavirinpregnancyregistry.com) maintains a registry of pregnancy-related exposures and advises all women to wait 6 months following discontinuation of ribavirin before attempting to get pregnant.

Following injection, maternal systemic exposure to ribavirin is 1000-fold higher than following secondary exposure to aerosolized drug [3,6]. Despite ribavirin being introduced systemically in the first trimester, it did not cause any congenital abnormalities or developmental defects in the infant. Although this report is limited by describing a single case it is, to the best of our knowledge, the first description of systemic maternal exposure during embryogenesis.

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