



Motherisk Update

Paternal use of ribavirin–interferon alpha 2B combination therapy before conception

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ABSTRACT

QUESTION One of my male patients is receiving ribavirin–interferon alpha 2B (Pegatron) combination therapy for chronic hepatitis C. His wife recently found out she is 6 weeks pregnant. They are concerned that the medications might have affected his sperm. How should I advise them?

ANSWER To the best of our knowledge, paternal exposure to ribavirin–interferon alpha 2B has no adverse effects on reproduction. Although we do not have sufficient information to confirm this, several pregnancies where the father had been exposed to these medications turned out fine. If an unexpected pregnancy occurs while the father is receiving this therapy, there is no medical indication for terminating the pregnancy.

RÉSUMÉ

QUESTION L'un de mes patients reçoit une thérapie combinée de ribavirine et d'interferon alpha 2B (Pegatron) pour une hépatite C chronique. Sa conjointe vient d'apprendre qu'elle est enceinte de six semaines. Ils s'inquiètent de l'effet de ces médicaments sur le sperme. Quels conseils devrais-je leur donner?

RÉPONSE Au meilleur de notre connaissance, l'exposition paternelle à la ribavirine–interferon alpha 2B n'a pas d'effet indésirable sur la reproduction. Même si nous n'avons pas suffisamment de renseignements pour le confirmer, plusieurs grossesses où le père avait été exposé à ces médicaments n'ont pas eu d'issue défavorable. Si une grossesse imprévue survient pendant que le père reçoit cette thérapie, il n'y a pas d'indication médicale justifiant de mettre un terme à cette grossesse.

Hepatitis C viral infection is among the leading causes of chronic liver disease in North America; an estimated 200 to 300 million people are affected worldwide.^{1,2} The current standard treatment for chronic hepatitis C is ribavirin–interferon alpha 2B combination therapy for 24 or 48 weeks.³ Outcomes of chronic hepatitis C improved considerably when this combination therapy was introduced.¹⁻¹⁰

Although this therapy is used by many people of childbearing age, we have little information on whether it has adverse effects on pregnancy. The adverse effects of these drugs found in animal

teratology studies¹¹⁻¹³ have led to ribavirin being contraindicated for women planning pregnancy and for men whose partners might become pregnant. Women should not be started on ribavirin–interferon alpha 2B combination therapy until the fact that they are not pregnant has been confirmed. Also, both male and female patients should use contraception for 6 months after discontinuing the treatment.¹⁴

Considering that half of all pregnancies in North America are unplanned,¹⁵ there is a good chance some fetuses will be exposed to these medications. If pregnancy occurs while either mother or father

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is receiving ribavirin–interferon alpha combination therapy, the parents might think they ought to terminate the pregnancy.

As use of this combination therapy increases, the Motherisk Program receives an increasing number of inquiries about paternal exposure to ribavirin–interferon alpha 2B. The product label clearly states that both male and female patients should use contraception for 6 months after therapy, so patients are greatly concerned when pregnancy occurs.

Possible mechanisms of toxicity

Paternal exposure to ribavirin. Ribavirin is a purine nucleoside that exerts its antiviral effects by inhibiting inosine 5'-monophosphate dehydrogenase. Ribavirin's primary antiviral mechanism of action against a model RNA virus is through lethal mutagenesis of the RNA virus genomes. Because ribavirin has the ability to interfere with the biosynthesis of guanine nucleotides, it could disrupt developing sperm or embryos. Ribavirin accumulates within the cells and is eliminated slowly from nonplasma compartments. The extensive accumulation of ribavirin in erythrocytes and other tissue and its slow clearance rate raise the possibility that it could accumulate in sperm in concentrations high enough to induce defects. In animal studies, ribavirin produced changes in sperm at subclinical doses. Another mechanism by which ribavirin treatment could theoretically affect embryo development is by being transmitted through seminal fluid.¹⁶

Paternal exposure to interferon alpha. Interferon alpha inhibits both cellular proliferation and protein synthesis. Interferon alpha has antiviral activity through its effects on protein synthesis and RNA degradation. Although no systematic studies have been published on paternal exposure to interferon alpha, there is potential for such exposure to affect sperm.

Current case reports

Although either ribavirin or interferon alpha could damage human embryos, no adverse effects have been described among offspring of women or men treated with combination therapy in the few human pregnancies where we know fetuses were exposed. No epidemiologic studies of paternal use of ribavirin alone, interferon alpha alone, or ribavirin–interferon alpha combination therapy have been published. Some case reports have described paternal exposure to ribavirin–interferon alpha within 6 months of conception.¹⁷⁻²⁰

Maddrey reported 15 cases of paternal exposure to ribavirin.¹⁸ Seven patients failed to attend follow-up appointments, two had healthy babies, four had spontaneous abortions, and two chose therapeutic abortions.

Hegenbarth et al reported two cases of paternal exposure to ribavirin–interferon alpha combination therapy within 6 months of conception.¹⁷ One patient received 1200 mg of ribavirin daily plus 6 mouse units (MU) of interferon alpha 2A every other day, and the other received 800 mg of ribavirin daily plus 6 MU of interferon alpha 2A every other day. Both had normal healthy babies; neurodevelopmental examination of the babies at 4 months yielded normal results.

Bianca and Ettore reported a case of periconceptional exposure to ribavirin–interferon alpha combination therapy.¹⁹ A male patient with chronic hepatitis C started combination therapy 6 weeks before conception. A normal healthy infant was born at term.

Out of seven men exposed to ribavirin–interferon alpha combination therapy (doses varied from 600 mg/d to 1200 mg/d) described by De Santis et al,²⁰ six had fathered pregnancies within 6 months of discontinuing therapy. No offspring had congenital defects; one aborted spontaneously. Seven healthy babies were born (one

patient had twins) with no complications during pregnancy or follow up, which ranged from 3 to 14 months after delivery.

Conclusion

These four case reports¹⁷⁻²⁰ showed no congenital malformations, 12 healthy infants, five miscarriages, and two therapeutic abortions. Although ribavirin is a potential teratogen, there seems to be no immediate reason for terminating pregnancy when a father has been exposed to it. These pregnancies can be continued under close monitoring, for example, with level 2 ultrasound scans. ❁

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Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. Dr Taguchi and Dr Ito are members of the Motherisk Program.

Do you have questions about the safety of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at (416) 813-7562; they will be addressed in future Motherisk Updates.

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