Alpha interferon and ribavirin impact on pregnancy

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Abstract

Infection with hepatitis C virus is a real problem of public health in developing countries especially because of increased number of intravenous drug users. Although the risk of mother-to-child transmission of HCV is less than 5%, the absence of an efficient prophylaxis of vertical transmission of HCV makes this problem important. Therapeutic regimens for HCV infection contain alpha interferon and ribavirin even after the introduction of the first class of direct acting antivirals. Both, alpha interferon and ribavirin are contraindicated during pregnancy, but sometimes fetal exposure at these drugs is reported. Moreover, not only maternal exposure can be dangerous for the offspring but also paternal exposure, if the subject was treated during pregnancy or 6 months after treatment discontinuation. The present review analyzes the data regarding safety of alpha interferon and ribavirin during pregnancy.

Keywords: *alpha-interferon, ribavirin, teratogenicity, pregnancy*

1. Hepatitis C virus infection in pregnant women

Infection with hepatitis C virus (HCV) is a problem of public health worldwide. More than 300 million people are infected with HCV worldwide with a variable prevalence in different regions[1]. In the United States the prevalence of HCV antibodies is around 2% in general population, while in adolescents population is around 0.4%, correlated especially with intravenous drug addiction[2].

The most important way of HCV spreading is through direct contact with infected blood and sometimes through other body fluids. The major explanations for HCV transmission worldwide are the use of unscreened blood and re-use of needles.

Viral hepatitis during pregnancy may increase the risk of maternal complications. In the same time a risk for mother-to-child transmission of HCV exists especially around time of delivery but also transplacental[3].

The mother-to-child transmission of HCV is defined by the presence of both HCV antibodies and HCV-RNA in infants. The overall rate of HCV mother-to-child transmission was appreciated around 5% but the co-infection with HIV increases the risk of mother-to-child transmission of HCV[4].

Regarding the indication of Caesarean sections and of breast-feeding in HCV infected women, EASL gave a B2 recommendation ("B - further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate and 2 - Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption"). The guidelines authors said that pregnant women with HCV hepatitis do not represent an indication for Caesarean sections because this technique does not seem to decrease the risk of HCV transmission. Mothers with chronic HCV hepatitis can breast-feed their children only if are negative for HIV infection[5].

The antenatal screening for HCV infection in order to prevent the mother-to-child transmission is controversial. The most guidelines recommend antenatal screening for HCV only for those at risk for HCV acquisition such as blood transfusions recipient before 1990, intravenous drug users, the patients under haemodialysis and HIV-infected subjects[6]. Therapeutic regimens recommended by the actual guidelines in HCV hepatitis contain pegylated interferon and ribavirin with duration according to therapeutic response[5].

An important issue of this therapeutic regimen is represented by the numerous side effects, some of them with life-threatening potential. Although the most studied side effects are hematological disorders, teratogenicity of these drugs are also very important because many young people are treated for HCV infection. Moreover, about 50% of the pregnancies are unplanned, exists a theoretical risk for some fetuses to be accidentally exposed to these medication. When pregnancy occurs while one of the parents is under medication for HCV infection, an abortion may be necessary. The labels of ribavirin and alpha interferon strongly recommend contraception during treatment and six months after the treatment discontinuation.

EASL guidelines for management of HCV infection strongly contraindicate the antiviral therapy during pregnancy or for couples unwilling to comply with adequate contraception[5].

Ribavirin is contraindicated in pregnant women because it's demonstrated teratogenicity on animal.

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What is more important and less known is the necessity of using contraception for 6 months after treatment discontinuation for both women and men whose partners may become pregnant[7,8].

The teratogenicity of interferon alpha was not clearly demonstrated.

The patients at childbearing age, treated for HCV infection must be informed for the teratogenicity risk before the treatment. Despite educational efforts are still reported cases of ribavirin and alpha interferon exposure during pregnancy. It is critical to understand the importance of counseling the patients treated for HCV hepatitis, before starting of treatment.

2. Interferon in pregnant and child-bearing age women

Perinatal transmission represents the major way of new-born infection with HCV in developed countries. The seroprevalence of anti-HCV antibodies in pregnant women was estimated between 1 and 8% and in the absence of HCV vaccine the prevention of vertical transmission of HCV is not possible. The risk of mother-to-child transmission of HCV is within the range of 1-5%. Caesarian-section and withholding breastfeeding did not seem to decrease the risk of HCV transmission[5].

Some studies regarding safety of alpha interferon were made on animal model. Li D et al. studied the safety of alpha interferon in transgenic mice during pregnancy. No adverse effects were observed in the offsprings of mice[9].

Until now were reported only a few cases of interferon exposure during pregnancy.

In 2002 Ozaslan E et al. published the case of a 26-year-old pregnant woman who developed HCV acute hepatitis in the 16th week of pregnancy and was treated with a total dose of 72 million units of alpha interferon. Twin premature infants were born trans-vaginally; at 18 months of age they were negative for HCV antibodies. The young woman achieved sustained virologic response. The authors reviewed other 6 cases of children born from mothers who received interferon during pregnancy without congenital anomalies[10].

Because interferon alpha is an important medication in other diseases than hepatitis, the safety of this drug during pregnancy was evaluated in pregnant women or in women of childbearing age with thrombocythemia or with chronic myelocytic leukemia.

Few cases of exposure to interferon alpha during pregnancy in women with thrombocythemia were reported. Five pregnant women who were treated with alpha interferon for essential thrombocythemia delivered normal infants, 2 premature new born and 3 full-terms new born. The children were not diagnosed with congenital anomalies after interferon alpha exposure. Four other pregnant women with essential thrombocythemia did not receive interferon therapy. All pregnancies were carried out: 3 intrauterine and one neonatal death[11].

In 2012 a systematic review of the fetal safety of interferon alpha was published in order to summarize all data about interferon alpha exposure during pregnancy for thrombocytemia. Among sixty-three interferon alpha exposed pregnant women were not reported major malformations or stillbirths. There were reported a case of spontaneous abortion and 13 preterm deliveries. Among seventy-one women without interferon therapy 65% had pregnancy loss, 4% of stillbirths and 5.6% of preterm delivery. This important recent paper showed that interferon does not increase the risk of congenital malformations. Regarding pregnant women with trombocythemia, interferon alpha therapy seems to have a protective effect against pregnancy loss[12].

3. Ribavirin in pregnant and child-bearing age women

Ribavirin is a FDA pregnancy category X product which is contraindicated in pregnant women. Because sometimes women at childbearing age are exposed to ribavirin during pregnancy or in the first six months after treatment discontinuation, from 2003 in United States was opened a program - the Ribavirin Pregnancy Registry. This program monitors the children born for mothers exposed to ribavirin directly, during pregnancy or during the 6 months after end of treatment or indirectly, by paternal use[13]. In 2010 the results between 2003 and 2009 were published by Roberts SS at al. In this period were registered 49 live births with direct exposure and 69 live births with indirect exposure to ribavirin. Six life-born infants with birth defects were listed. Three children were related to maternal exposure and three to paternal one. The authors' conclusions did not indicate an excess of malformation in children exposed to ribavirin[14].

Labarga P et al. presented the case of a HCV-HIV co-infected pregnant woman who received antiviral treatment with pegylated interferon, ribavirin and antiretrovirals during the first 16 weeks of pregnancy. The new-born was neither HIV, nor HCV-infected and were not detected any malformation[15].

Other few cases of ribavirin exposure during pregnancy were reported in women who were not infected with HCV but developed other severe infections. In 2003 five live born infants from mothers with severe respiratory acute syndrome were exposed to ribavirin. The authors did not take into account the teratogenicity of ribavirin and did not mention if any malformations were reported. Two infants developed intestinal damages which were not correlated to ribavirin administration[16].

In 2006 another healthy child exposed to ribavirin in the first trimester of life was described. The mother received injectable ribavirin for a severe acute respiratory syndrome[17].

Recently, a case of Lassa hemorrhagic fever in a pregnant woman from Sierra Leone who received ribavirin was reported. The maternal outcome was good but the authors did not mention any congenital damages related to ribavirin in new born[18].

4. Paternal use of interferon

The possible effects of alpha-interferon on spermatogenesis and quality of sperm were evaluated in rats. Daily sperm production, epididymal sperm concentration and serum testosterone levels were increased after alpha-interferon administration. Alpha-interferon seems to improve spermatogenesis on animal model and could be an alternative therapy for male infertility[19].

Until now were not published systematic studies which can demonstrated the effect of alpha-interferon on sperm. Because interferon alpha inhibits protein synthesis, produces RNA degradation and inhibits cellular proliferation was speculated a potential risk of sperm damages[20].

5. Paternal use of ribavirin

It is well-known the potential of many drugs taken during pregnancy to produce damages of the offspring which may conduct to spontaneous abortion, stillbirths and congenital malformations. Despite multitude of study conducted in this area, more than 60% of congenital malformations have unknown origin. That is way some studies have taken into account the possibility that the male exposure to some drugs could lead to offspring damages. Both animal studies and epidemiological studies were conducted in order to demonstrate the role of paternal exposure to drugs and congenital malformations.

One of the mechanisms of male reproductive toxicity is non-genetic mechanism, due to a drug presence in seminal fluid.

Ribavirin interferes with the guanine nucleotides synthesis by inhibiting inosine 5'- monophosphate dehydrogenase which can conduct to developing sperm alteration and disruption of embryos. Ribavirin is accumulated in interstitial tissue, within the germinal cells and is than eliminated in sperm in high enough concentrations to produce damages. In the same time, ribavirin can be transmitted directly by seminal fluid[21].

Hofer H et al. demonstrated in 2010 that concentration of ribavirin in seminal fluid is twofold higher than serum levels. Seminal fluid from 15 male patients treated for HCV infections was analyzed regarding sperm concentration, motility and morphology at baseline, week 4 and week 12. The authors emphasized the role of contraception during treatment with ribavirin[22].

Semen abnormalities were detected even at baseline demonstrating the role of HCV infection. These abnormalities were decreased during antiviral therapy. From 15 analyzed patients, HCV-RNA was detectable in the seminal fluid of two cases at baseline and was undetectable in week 4 and 12 for all patients[22].

Pecou S et al. reported for the first time in 2009 the qualitative alterations of spermatogenesis which persisted 8 months after the treatment discontinuation. They reported a case of a 37-year-old male treated for HCV infection that had an increasing round cell/spermatozoa ratio and a decreasing number of motile sperm during the treatment. The authors recommended that the contraception period after the treatment interruption may be even longer than six months[23].

In 2006 Durazzo M et al. evaluated the influences of HCV infection and antiviral treatment on reproductive function in male. Seminal parameters and reproductive hormonal serum levels are comparatively analyzed between men infected with HCV and healthy volunteers. These parameters were evaluated in HCV infected subjects at baseline and after six and twelve months of pegylated interferon plus ribavirin therapy. HCV infected patients had worse spermatic parameters than healthy volunteers. Therapy seems to improve the spermatic function by increasing inhibin B levels and by improving hormonal pattern in responders[24].

The toxic effects of ribavirin on reproductive parameters were evaluated also on animal model. Ribavirin induced the formation of vacuoles and gaps in seminiferous epithelium and determined the formation of micro-cephalic sperms in Wistar rats. These morphological changes were recovered after a medium period of three months. The serum level of testosterone was also analyzed. A decreased of testosterone serum level was also observed, without recovery after ribavirin discontinuation[25]. It was also demonstrated the ribavirin mutagenic transient effect on germ cells of rats[26].

However, despite possible damages of sperm, in the few pregnancies with paternal exposure to ribavirin have not been described life births with congenital malformation.

In 1999 Maddrey reported 15 cases of indirect exposure to ribavirin. Only 8 patients were monitored: two had healthy new-borns, two chose abortion and four had spontaneous abortions[27]. Two years later, in 2001, Hegenbarth et al. reported other two cases of paternal exposure to ribavirin, both were healthy children[28]. In 2003 Bianca S et al. reported a normal healthy child born after indirect exposure to ribavirin[29]. De Santis et al. described seven newborns with paternal exposure to ribavirin during intrauterine life. Seven preg-

nant women whose husbands received ribavirin within 6 months of follow-up were monitored. One of them had spontaneous abortion and six had healthy babies (one had twins)[30].

In 2010 was published the largest study regarding pregnancy monitoring after ribavirin exposure. The Ribavirin Pregnancy Registry monitored pregnant women with direct or indirect exposure to ribavirin. Between 2003 and 2009, 69 live births with indirect exposure to ribavirin were reported. Three babies had malformation (4.3%) but without statistical significance[14].

6. Conclusion remarks and future outlook

The antiviral treatment for HCV hepatitis with alpha interferon and ribavirin is contraindicated during pregnancy. Moreover, an efficient contraception is recommended during pregnancy and 6 months after the treatment discontinuation in both maternal and paternal exposure at this medication. However, there were not observed an increased number of congenital malformations related to alpha interferon and ribavirin exposure during pregnancy in the very few cases reported until now. Although there were not reported an increased number of malformations after exposure at these drugs, we can suppose that could exist unreported cases. It is difficult to recommend abortion if an unplanned pregnancy occurs during the treatment or in the first 6 months after treatment for HCV hepatitis. The couple must be correctly informed about the risk in order to be able to make a decision. ■

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