

REVIEW

SEXUAL TRANSMISSION OF HEPATITIS C

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SUMMARY

It is generally agreed that the hepatitis C virus (HCV) can be efficiently transmitted parenterally, although data on viral transmission by sexual or non-sexual intrafamilial contact are conflicting. Since data collection began in 1989, the first study dealt with the risk of sexual transmission among multiple sex partners. Other investigations followed, emphasizing that risk increases in specific groups such as patients co-infected with HIV and HBV, sex workers, homosexuals, illicit drug users and patients attended at sexually transmittable disease clinics.

The question arises as to what might be the risk for monogamous heterosexuals in the general population, in which one of the partners has HCV?

The literature provides overall rates that vary from zero to 27%; however, most studies affirm that the chances of sexual transmission are low or almost null, with rates for this mode fluctuating from zero to 3%. Intrafamilial transmission is strongly considered but inconclusive, since when mentioning transmission between sex partners within the same household, specific situations also should be considered, such as the sharing of personal hygiene items, like razorblades, toothbrushes, nail clippers and manicure pliers, which are important risk factors in HCV transmission. In this review, we discuss the hypotheses of sexual and/or intrafamilial transmission.

KEYWORDS: Hepatitis C; Transmission; Sexual; Intrafamilial.

Patients infected by HCV frequently question whether their infection can be transmitted to their sexual partners, and whether HCV can be transmitted through sexual relations. Common sense suggests that HCV like HBV and HIV can be transmitted through sexual contact, but what is the degree of risk? Does it depend on the population studied? Can risk behavior alter contamination potential^{27,34,74}?

Classically, parenteral exposition unites many risk factors that are relevant for HCV transmission, such as the use of illegal drugs, hemodialysis, blood transfusion and blood derivatives, tattoos, organ transplants, acupuncture, sharing of straws for drug inhalation, and accidents in health-care workers^{12,26,49,58,71,89}.

Convincing evidence for the sexual transmission of HCV requires a history of couples having lived together in sexual activity, the absence of other opportunities for infection, and genetic evidence on the virus, demonstrating that both partners are infected by a virus with very similar genomic sequences. The possession of quality information concerning these questions can aid in providing answers to these issues. However, few studies meet these criteria satisfactorily^{22,69,85}.

ALTER *et al.* (1989)² presented the first study in which the possibility of HCV transmission was discussed, and considered multiple sex partners as a risk factor. However, the contribution of sexually transmitted HCV remains controversial. In the United States, the Centers for Disease control and Prevention (CDC) estimates that between 20 to 25% of the transmission indexes are associated with sexual contact, although the numbers discussed worldwide fluctuate since many different population are involved^{2,15,48}.

The information available on the sexual transmission of HCV varies considerably; the numbers reported lying between zero and 27%. However, the majority of studies mention rates of between zero and 3%. These low indexes, associated with rare risk factors, suggest that sexual transmission presents a minimal or negligible risk^{18,30,31,44,49,51,54,69,82,83,92}.

Studies that discuss specific groups, such as those who attend clinics for sexually transmitted diseases like drug abusers, homosexuals and sex workers, reveal findings that differ from those of the general population, and the risks of sexual transmission of HCV increase considerably^{12,15,18,23,25,26,37,51,61,65,68,69,83,85,91}.

GAMBOTTI *et al.* (2005)²⁷ identified 29 cases of acute hepatitis C that occurred between 2001 and 2004 in a population of positive HIV men who had sex with other males, and performed risk behavior such as unprotected sex or sex with multiple partners, revealing percentages of seroconversion for HCV above that of the general population²⁷.

In analyzing a cohort of 1,038 homosexual males, BODSWORTH *et al.* (1996)⁴ found 7.6% to be positive for anti-HCV, and suggested that immunological suppression caused by HIV might facilitate acquisition of the infection. Investigators such as FILIPPINI *et al.* (2001)²³ affirm that the risk of sexual transmission is greater in the case of HIV-HCV co-infection^{4,23}.

In a review article, BONACINI & PUOTI (2000)⁵ presented that stable partners of HCV infected patients have a higher risk of HCV infection than partners of HCV negative index case. HIV coinfection in the index case was initially thought to enhance sexual transmission. However, other studies did not confirm this initial impression⁵.

In Canada, when investigating the risk of sexual transmission of HCV and HIV among users of non-injectable drugs and their sexual partners, it was noted that in groups with low risk behavior the potential existed for the sexual transmission of HCV⁵⁶.

When considering patients attended at hepatology clinics and who do not belong to groups with risk behavior, but who are HCV carriers, and their sexual partners, what might be the risk of these, non-carrier partners becoming infected through sexual activity? This question must be considered and evaluated carefully^{69,76,92}.

One group that arouses much curiosity is the HCV positive patients who do not present an identifiable risk factor for HCV infection, which is on average of 30-40% of patients. Probably sexual transmission, like other forms of human contact can play a significant role within this group of patients^{6,16,28,30,39,57,68,76}.

In Australia, where notifications of Hepatitis C cases were evaluated, the risk factors related to HCV transmission showed indexes of less than 2%. The research mentions that seropositivity between sexual partners was greater than between other individuals who had non-sexual contact and resided in the same household¹⁹.

NEUMAYR *et al.* (1999)⁵⁷, after evaluating genotypes among eight couples, reported just two in agreement, only one of who presented another evident risk factor, showing that sexual transmission is possible but infrequent among monogamous mates of chronic HCV carriers. KAO *et al.* (1996)³⁸ found an index of 17% among 100 positive anti-HCV couples. Of these, 11 presented the same 1b genotype^{38,57}.

TANAKA *et al.* (1997)⁸² observed that the spouses of sex partners who were HCV carriers showed a 2-fold risk of contracting the disease than the spouses of partners who were HCV negative. SOTO *et al.* (1994)⁷⁹, in a multicentric study, evaluated 423 heterosexual partners with a case index reactive for anti-HCV, and suggested that the infection could be transmitted sexually, but with little efficiency. However, co-infection by HIV may increase these values. MARINCOVICH *et al.* (2003)⁴⁴, on evaluating a cohort of 171 heterosexuals, initially seropositive for HCV and HIV, suggested that the sexual transmission

of HCV is extremely low or even null, and no couple in the population studied converted seropositively for HCV^{44,79,82}.

The sexual and intrafamilial transmission of HBV has been well documented, but the same issue for HCV does not appear to have been established. We also know that the transmission of HBV and HIV is considerably greater than that of HCV; however, the number of people who could acquire Hepatitis C by sexual means should not be neglected^{10,15,17,23,24,28,40,51,85,86}.

Comparison between sex partners and other family members residing with the same household, having a HCV carrier as a reference, shows that intrafamilial contact is an important factor in the transmission of HCV. Cultural habits differ from one population to another and can interfere in the results of epidemiological studies that involve HCV transmission.

In a study by DIAGO *et al.* (1996)¹⁷ the incidence of anti-HCV for sex partners of index cases was 7.6% (30/394), and for other members of the family was 3.3% (34/1057)¹⁷.

In CHANG'S *et al.* study (1994)¹⁰ of 307 families of HCV-carrier patients, 28% presented anti-HCV positive mates, a higher percentage, compared to children and other household contacts of HCV index case (6.4%) ($p < 0.001$). Anti-HCV positivity was 23% in husbands who presented wives as an index case, and 29% in wives who presented husbands as an index case¹⁰.

Identification, the means of transmission, and evaluation of HCV prevalence among family members are very important factors as concern prevention of the dissemination of HCV infection in endemic areas⁷³.

Egypt is a country endemic for HCV infection. In one population study, 669 parturient women were investigated of whom 94 were positive in tests for detecting anti-HCV antibodies subsequently 35 genomic sequences of HCV were genotyped and the homologies among them established. The outcome was that 33 sequences exhibited the same genotype, 30 showed 100% similarity, two 97% and one 91% similarity. The NS3 region of the HCV genome was also sequenced. The index for children was low compared to couples. In this study, sexual transmission seems to play an important role in the intrafamilial transmission of HCV^{41,43}.

OKAYAMA *et al.* (2002)⁶⁰ evaluated 973 subjects in Japan in an area considered to be endemic for HCV, showing that 23% were anti-HCV positive. This population was accompanied, and in an 11-month period, 14 partners seroconverted. Of these, five had a history of being with a mate who was a HCV carrier, and six did not. There was no statistically correlation, and sexual transmission was not considered likely⁶⁰.

In evaluating risk factors for HCV infection in 109 cases and 250 family members of patients with chronic hepatitis in Korea, KIM *et al.* (1998)⁴⁰ diagnosed HCV infection only in one spouse (1.2%) and in no children, concluding that the degree of sexual or familial transmission of HCV infection is extremely low⁴⁰.

A report of intrafamilial transmission in Italy mentions 8% positive

cases among family members of HCV positive patients, against less than 1% in the general population. Another study from researchers at the CDC, mentions 22.6% as the risk for acquisition from infection through sexual relations and family-member contact, after evaluating 206 HCV carrier patients^{3,36}.

HOU *et al.* (1995)³⁴ evaluated the spouses of patients undergoing hemodialysis, and observed an increase in HCV infection compared to the risk of other family members living in the same household³⁴.

DE MERCATO *et al.* (1996)¹⁶ in his study, which differs from others, found no positive results in children who lived in the same household with HCV-positive patients; however, in the same population, 22% of spouses were positive. These authors concluded that sexual transmission should not be excluded, and that the high prevalence was related to the length of time the couples had lived together¹⁶.

The question as to the length of time necessary for couples to live together to establish sexual transmission of HCV is another controversial issue that should be emphasized. There are divergent and convincing reports in the literature that discuss both acute and chronic infection, whenever possible evidence of sexual transmission arises.

In a review article ROONEY & GILSON (1998)⁶⁸ report a risk estimate for HCV infection of 1.5 (CI 1.05-2.2) per decade of marriage, and that women with HCV-positive partners have a 3.7 fold chance of contracting the disease. Other studies revealed that, in addition to familial contact and sexual behavior, the sharing of items of personal use, such as razor blades, tooth brushes, nail clippers and manicure pliers can be important in the intrafamilial transmission of hepatitis C^{12,14,16,17,26,29,38,40,49,51,53,55,59,68,73,74,77,78,83,85}.

SCOTTO *et al.* (1996)⁷⁵ found that 8.43% of 83 sex partners studied were HCV positive. Curiously, no partner of the ten patients who underwent dialysis was anti-HCV positive. In mates of patients with chronic liver disease, five in 31 (16.12%) were positive, and in mates of patients with anti-HCV two in 42 (4.7%) were positive⁷⁵.

STROFFOLINI *et al.* (2001)⁸¹ concluded that despite eight of 13 couples presenting the same viral type, sexual transmission was considered low, and the sharing of syringes appeared to be the most effective route for virus transmission in couples⁸¹.

Doubts have been raised regarding the necessity of couples living together for long periods of time to increase the risk of sexual transmission of HCV^{66,67}. In a report by CAPELLI *et al.* (1997)⁷ a female repeat donor was surprised to learn that she was PCR-HCV positive, sometime between the two donations. She noted that she lived with a sexual partner who was a chronic HCV carrier. The similarity of the virus in the couple was 93.4% (E2/NS1 region). No other risk factor was identified⁷.

Another report, with strong indications of sexual transmission over a short time period in a couple living together, with one sex partner being HCV-positive, showed a double infection, with types two and four present in both partners. This was the first published case of the transmission of two different types of HCV⁷⁴.

In defense of the need for long periods of living together to justify the transmission of HCV, HERSHOW *et al.* (1998)³³ found significant risk factors for HCV infection when considering promiscuous sex partners, sex partners of drug users, associated sexually transmitted diseases, paid sex and a long period of living together with a HCV-positive partner³³.

The sexual transmission of HCV involves a wide range of issues that should be considered together when discussing the subject. Among this issue is the number of sex partners¹².

MELE *et al.* (1999)⁴⁷ analyzed the number of sex partners in the transmission of HCV and found the risk to be two-fold higher for those who reported having two sex partners, and 2.8-fold higher for those who reported three partners. These groups were compared to reports on those with less than two partners, which suggests that sexual transmission may play an important role in the transmission of hepatitis C in Italy⁴⁷. Further, SALLERAS *et al.* (1997)⁷² reported on the number of sex partner, showing an increase in the risk of HCV transmission that was 14-fold greater in those with four partners or more, and only three-fold greater in those who reported two or three partners. This risk was compared with that for patients who mentioned having only one sex partner. The authors note that sexual transmission should be considered as a mode of HCV transmission in patients who do not show other means of parenteral exposition^{32,35}.

There have been few reports from Brazil on the sexual transmission of HCV. Among the most important, TENGAN *et al.* (2001)⁸⁴ evaluated 154 blood donors who presented a positive serological reaction for HCV and their sex partners. In this population, 11.76% of the partners were considered to be currently or previously infected by HCV, suggesting that the high prevalence of infection among these partners could be attributed partially to sexual transmission. In another important study, CAVALHEIRO (2004)⁹ recruited 45 couples with a diagnosis of hepatitis C, choosing 24 in whom both partners presented viremia, allowing a phylogenetic analysis of the genomic chains of HCV between couples. The findings of this study revealed a similarity of 98.3% between the partners in 22 (91.7%) of couples using the NS5b region for analysis. Further a high index of sharing personal items was evident, and was considered a confounding factor, making it difficult to conclude that transmission was strictly through sexual means^{9,84}.

SOUTO *et al.* (1994)⁸⁰ addressing the importance of risk factors in the acquisition of HCV infection in 780 inhabitants of the South Amazon region found no signs that sexual transmission might contribute to the prevalence of anti-HCV found 2.4%. In a study performed at the Hospital das Clínicas of the University of São Paulo, Brazil, a prevalence of 20.2% RNA-HCV positive couples was reported, with one of the partners already known to be infected by HCV. There was a HCV genotype concordance in 16 of the 20 cases studied, with a greater frequency of genotype one^{48,64,80}.

MESQUITA *et al.* (1997)⁵⁰ examined a population of Brazilian prostitutes and their clients, analyzing the risk factors associated with the transmission of hepatitis C, suggesting that sex transmission plays an important role in the epidemiology of HCV, mainly when promiscuous sexual behavior is concerned. The prevalence of HCV in this population was 1.5%, index that reaches around 2.2% in blood

banks. The authors concluded that sexual transmission plays an important role in the propagation of HCV infection in humans. PASSOS *et al.* (2002)⁶² concluded that sexual and perinatal transmission was low among 409 patients from an assisted reproduction clinic. In 1995, FIGUEIREDO *et al.*²² analyzed 83 couples, and the incidence of 2.4% in this group suggested sexual transmission. The authors considered this route to be probable but not very efficient^{22,50,62,88}.

Dwelling further on the subject of sex partner numbers, involving the important risk group of paid sex, there are findings that differ from the general population⁴⁵. NAKASHIMA *et al.* (1996)⁵³ in Japan tested 244 prostitutes for HCV, 10.1% presented positive serology, while women recruited from blood banks presented an index of 0.8%. Also, with more years of activity, the chances of contracting the virus were greater⁵³.

LAURENT *et al.* (2001)⁴² in a study from the Republic of Congo affirmed that the sexual transmission of HCV among prostitutes in this population was not relevant, finding only significant transmission among women who also presented an associated sexually transmittable disease⁴².

Another question concerning the sexual transmission of HCV is the presence of the virus in secretions, saliva^{20,21}, semen^{8,59} and menstrual blood⁷⁸. Some studies raise the issue and discuss the most probable pathway of infection, and whether it is from men to women or from women to men. HCV can be isolated from both semen and vaginal secretion; however, there seems to be a greater potential for transmission from men to women. Certainly, trauma to the mucosa during sexual intercourse increases the risk of viral transmission, as do the high levels of viremia and positive PCR for semen. Technical difficulties should also be considered regarding PCR-HCV for semen, which can obscure a positive diagnosis^{85,90}.

The semen of 35 men was evaluated, and five presented a positive PCR-HCV. CASSUTO *et al.* (2002)⁸ and others note the difficulty with inhibitor transport when handling samples during PCR-HCV, can lead to false-negative results⁸.

SILVERMAN *et al.* (1994)⁷⁸ examined the menstrual blood of ten women chronically infected with HCV, and all samples were HCV-RNA positive. Their study suggested a mechanism possibly involved in the route of female-male sexual transmission of HCV infection⁷⁸.

Curiously, on evaluating the possible consequences of an accident, in which women had received anti-D immunoglobulin contaminated with hepatitis C virus, MEISEL *et al.* (1995)⁴⁶ on re-examination 10-15 years later, together with 94 husbands, found no evidence of HCV transmission to these men. This study reinforces the hypothesis that infection from woman to man is much less likely than the contrary⁴⁶.

The presence of HCV in saliva and the risk of transmission were evaluated by FABRIS *et al.* (1999)²⁰ who concluded that the presence of HCV in this fluid constitutes a necessary condition, but was insufficient for transmission. The study showed the presence of the virus at high levels in saliva fractions from chronic HCV carriers, but these findings were not associated with an increase in the risk of HCV transmission among sexual partners²⁰.

Epidemiological studies with virological support on the sexual transmission of HCV are not common in the literature, and the majority of studies refer to small numbers and report on acute transmissions in isolated cases. The region of the virus examined also varies from one study to another⁸⁵.

THOMAS *et al.* (1995)⁸⁷ investigated evidence of sexual transmission of HCV in a clinic for sexually transmittable diseases in Baltimore. The degree of homology, when the hypervariable (HVR1) region was evaluated at the junction between the E1 and NS1/E2 regions of the HCV was 94.4% for three couples compared to randomly selected samples that showed values significantly below 82.4%. The homology of these sequences indicates the common source of HCV infection, strongly suggesting sexual transmission. Women who had HCV positive partners presented indexes of infection 3.7-fold greater than those with HCV-negative partners⁸⁷.

MORSICA *et al.* (2001)⁵² on evaluating a case of acute HCV infection, found 94.9% similarity in the E2/HCV region, where the only likely source was sexual transmission⁵².

CHAYAMA *et al.* (1995)¹¹ analyzed the E1/HCV region in eight couples that had the same genotype. In five, the phylogenetic analysis showed a high similarity of > 97% with a much lower homology for the other three, of around 91-92%. The authors conclude that these data strongly suggest the occurrence of HCV transmission in these couples¹¹.

WILLIAMS *et al.* (2003)⁹⁰ researchers at the CDC Viral Hepatitis Division, accompanied 263 cases of acute hepatitis C; 13% of these cases reported sexual exposure as the sole risk factor in the acquisition of the disease. Serum samples of seven of 24 positive partners were analyzed, and five showed concordance of the genotype with identity in the genomic sequence of 97.8 to 99.3%. The relationships in these couples support sexual activity as a mode of HCV transmission⁹⁰.

PIAZZA *et al.* (1997)⁶³ accompanied 884 couples, with an inclusion criterion of negative PCR-HCV in mates of patients with chronic hepatitis C. These sex partners were accompanied for a period of two and a half years, seven becoming positive by PCR-HCV reaction. A strict homologous link was found in four cases and the percentage of homology was close or equal to 100% in the 5'UTR and Core sequences and about 70% in the hypervariable region 1 fragment. In the other three cases there was a percentage of homology between 90% and 95% in the 5'UTR and the Core sequences and between 37% and 50% in the hypervariable 1 region. This study concluded that hepatitis C is sexually transmittable⁶³.

ROSS *et al.* (1999)⁷⁰ on evaluating a couple whose phylogenetic study between viruses was 100% similarity, considering a Core-HCV region, noted that the results of the epidemiological inquiry and analysis of the viral genome are complementary components that provide evidence for the sexual transmission of HCV⁷⁰.

The homology among the genomic sequences merely suggests the same source of infection in partners. However, it does not allow us to confirm where and how the infection was acquired, whether by an external source like the sharing of items of personal hygiene or through intercourse^{65,85}.

In conclusion, it seems that the sexual transmission of HCV does take place, although with an efficiency much lower than seen for other viruses such as HBV or HIV. In addition to factors like co-infection with HIV and an association with sexually transmittable diseases, it also appears that the type of sexual activity can increase the efficiency of HCV transmission by sexual means.

RESUMO

Transmissão sexual da hepatite C

A eficiência da transmissão parenteral da hepatite C é consenso, porém dados na literatura sobre transmissão sexual e intrafamiliar são conflitantes.

Data de 1989 o primeiro trabalho que relaciona o risco de transmissão sexual a múltiplos parceiros sexuais, na seqüência, outros estudos também reforçam que os riscos aumentam em populações específicas como co-infectados HIV, HBV, profissionais do sexo, homossexuais, usuários de drogas ilícitas e populações de clínicas de doenças sexualmente transmissíveis.

Agora, na população geral qual seria o risco para casais monogâmicos heterossexuais onde um dos cônjuges apresenta a infecção pelo HCV? A literatura apresenta números que vão de zero a 27%, porém a maioria dos trabalhos afirma que as chances de transmissão são baixas ou quase nulas e aqui as porcentagens oscilam entre 0% e 3%. A transmissão intradomiciliar é fortemente considerada e mencionada como fator de confusão quando se menciona transmissão entre casais, pois se deve considerar que o compartilhamento de utensílios de higiene pessoal como lâmina de barbear, escova de dente, alicates de manicure e cortadores de unhas atuam como fator de risco importante para a transmissão do HCV dentro do domicílio. Transmissão sexual e/ou transmissão intrafamiliar, esta revisão trás à tona ambas hipóteses discutidas em diversos trabalhos pelo mundo.

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