Risk of Hepatitis C Virus Transmission From an Infected Gynecologist to Patients

Results of a 7-Year Retrospective Investigation

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Background: Currently, it is not known how often hepatitis C virus (HCV) is transmitted from infected health care workers to patients during medical care. In the present investigation, we tried to determine the rate of provider-to-patient transmission of HCV among former patients of an HCV-positive gynecologist after it was proven that he infected one of his patients with HCV during a cesarean section.

Methods: All 2907 women who had been operated on by the HCV-positive gynecologist between July 1993 and March 2000 were notified about potential exposure and were offered free counseling and testing. The crucial differentiation between HCV transmissions caused by the gynecologist and infections contracted from other sources was achieved by epidemiological investigations, nucleotide sequencing, and phylogenetic analysis.

Results: Of the 2907 women affected, 78.6% could be screened for markers of HCV infection. Seven of these former patients were found to have HCV. Phylogenetic analysis of HCV sequences from the gynecologist and the women did not indicate that the virus strains were linked. Therefore, no further iatrogenic HCV infections caused by the gynecologist could be detected. The resulting overall HCV transmission rate was 0.04% (1 per 2286; 95% confidence interval, 0.008%-0.25%).

Conclusion: To our knowledge, this is the largest retrospective investigation of the risk of provider-to-patient transmission of HCV conducted so far. Our findings support the notion that such transmissions are relatively rare events and might provide a basis for future recommendations on the management of HCV-infected health care workers.

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PATIENTS AND METHODS

SURGICAL PRACTICE EVALUATION

Interviews were conducted with the gynaecologist and the operating department personnel to collect information about his operating procedures, frequency and nature of percutaneous injuries, glove changing habits, and the adherence to so-called universal precautions.21 Other members of the teams, who regularly worked with the gynaecologist, were also asked about his surgical practices.

RETROSPECTIVE INVESTIGATION

A list of former surgical patients was developed from operating department records. A master patient file was created containing demographic and procedural information on the gynaecological and obstetric operations. Based on previous classifications,22,23 the frequency of percutaneous injuries sustained by surgeons,24-26 and the rate of glove perforations reported for gynaecological and obstetric procedures,27-31 patients were grouped according to “high,” “medium,” or “low” risk of exposure to HCV by the type of operation. For instance, major gynaecological surgery involving laparotomy, all hysterectomies, major repairs, and cesarean sections were considered high risk; cone biopsies, pelvicoscopic procedures, perineal sutures, and episiotomies were considered medium risk; and dilatation, curettage, and termination of pregnancy, low risk.

A letter of notification was sent to all 2907 women who had been operated on by the gynaecologist explaining the possibility of HCV exposure during hospitalization. The women were offered free, anonymous counseling and HCV testing. These services were available at Itzehoe Academic Teaching Hospital and could be accessed by calling a toll-free telephone number for an appointment. Registration offices were contacted to obtain current mailing addresses for patients whose letters were returned as undeliverable. To support responses to the mailing, a news release was issued in local papers and all physicians of the county were informed by a separate letter. The retrospective investigation was conducted in accordance with the principles of the Declaration of Helsinki. The costs were estimated based on documented personnel hours at each institution involved, billing records for special services, and the numbers of HCV antibody tests and molecular analyses performed.15

VIROLOGICAL AND MOLECULAR ANALYSES

Blood samples were centrifuged within 2 hours after venipuncture and the sera were frozen and stored until analysis. Antibodies against HCV were identified by third-generation enzyme-linked immunosorbent assay (Sanofi Diagnostics Pasteur Inc, Freiburg, Germany). Reactivity was confirmed by immunoblot analysis (Mikrogen, Munich, Germany). Patients whose sera were initially found repeatedly reactive in enzyme-linked immunosorbent assay but showed indeterminate results in immunoblot analysis were retested after 3 and 6 months. Hepatitis C virus RNA was detected by Roche Amplicor 2.0 (Roche Diagnostics, Mannheim, Germany) or by VERSANT HCV RNA qualitative assay (Bayer Diagnostics, Emeryville, Calif). Seventy-six individuals negative for HCV antibodies who still could have been in the incubation stage of acute HCV infection (lasting up to 26 weeks35) and 22 patients receiving immuno-suppressive therapy were screened for the presence of HCV RNA by nucleic acid amplification techniques. Hepatitis C virus RNA was quantified by VERSANT 3.0 b-DNA Assay (Bayer Diagnostics). Typing of HCV isolates was performed as described in full details elsewhere.34,35 Serotyping was performed with Murex HCV Serotyping 1-6 Assay (Abbott Laboratories, Wiesbaden, Germany) according to the manufacturer’s instructions. The primer sequences used for amplification of the HVR 1 of subtype 1b isolates were as follows: HVRO3 (nucleotides nt 1290 to 1310, numbering according to Takamizawa et al36), 5’-TGGGATATGATGATGAACCC (first polymerase chain reaction [PCR]); HVRO3 (nt 2007 to 2027), 5’-TCCGGCA(C, T)GTCTTA[A, G]GTGAACCC (reverse transcribease and first PCR); HVRI5 (nt 1326 to 1346), 5’-CTAAGTTGTTGCAG[C, T][A, G]TC (second PCR); HVRI3 (nt 1782 to 1802), 5’-CGCGTAATGCGAGGCAATA[A, T, G]GG (second PCR). Amplification of the HCV core region was performed as described previously.34,35 As area controls, 10 HCV isolates were obtained from patients within a radius of approximately 400 km from the hospital.37 Products of the second PCR were purified from the agarose gel (QiAquick PCR Purification Kit; QiAGEN, Hilden, Germany) and were subjected to direct sequencing in both directions (Dye Terminator DNA Sequencing Kit, Perkin-Elmer, Norwalk, Conn.).

To prevent possible cross-contaminations between the samples, highly stringent procedures as recommended by Kwok and Higuchi38 were applied for nucleic acid extraction and amplification. There was also a strict physical separation between the samples, since the experimental procedures on the sera were run several weeks apart. The stock of PCR primers for the amplification of HCV HVR 1 had not been used previously in our laboratory. Numerous HCV RNA–negative sera were analyzed in parallel with the samples. Hepatitis C virus core and HVR 1 sequences obtained from the surgeon’s and the patients’ samples have been submitted to GenBank (http://www.ncbi.nlm.nih.gov; accession numbers AF350912 through AF350922).

For statistical analysis, a matrix of nucleotide distances was calculated by Kimura’s 2-parameter method.39 Phylogenetic trees were constructed with the unweighted pair grouping method with arithmetic mean and neighbor-joining algorithms on the previous sets of pairwise distances (package PHYLIB, version 3.5; Joseph Felsenstein, PhD, 1993, distributed by Dr Felsenstein, University of Washington, Seattle). Significance of the grouping was evaluated by bootstrapping (1000 replicates). If more than 75% of the trees constructed from these resampled data were essentially similar to the tree generated from the original set, the topology was considered stable.
gist at Itzehoe Academic Teaching Hospital, Itzehoe, Germany. Serum samples obtained on March 3, 2000 (patient), and March 27, 2000 (gynecologist), were used for molecular biological analyses. Nucleotide sequencing of a core fragment and the hypervariable region 1 (HVR 1) of the HCV genome with subsequent phylogenetic analysis demonstrated the identity of the HCV subtype 1b strains isolated from the surgeon and the patient (see the “Results” section). Thus, it was proven that the highly viremic surgeon (260 000 IU/mL when tested in March 2000) had transmitted the virus to the patient during the cesarean section. A special investigation team was set up to manage the incident. This team included representatives from the hospital, the local public health administration, and the German National Reference Centre for Hepatitis C. Based on the findings of the initial investigation, it was decided to evaluate retrospectively the surgeon’s practice and to identify all patients who had been operated on by him between July 1, 1993 (the day when he started to work in the hospital), and March 15, 2000 (the day when he stopped operating). All women who were his surgical patients were offered free counseling and HCV testing.

## RESULTS

### SURGICAL PRACTICE EVALUATION

Surgical standard apparel were an overall, mask, hood, and gloves. Double gloves and glasses were only worn occasionally. Instruments were passed directly to the gynecologist’s hand by a scrub nurse during the operations. The gynecologist changed gloves when he noticed an interruption in their integrity. Percutaneous injuries predominantly occurred during deep pelvic surgery and cesarean sections, but neither the gynecologist nor his colleagues were able to give accurate estimates of their frequency. He could not recall any occasion when he bled into a patient’s wound. Interviews with other members of the operating teams corroborated the gynecologist’s recollections and failed to detect breaches of standard infection-control guidelines. Regarding the cesarean section on December 22, 1999, there were no unusual incidents documented in the relevant records, and the gynecologist as well as the members of the operating team could not recall any specific circumstances that might have caused HCV transmission to the patient.

### RETROSPECTIVE INVESTIGATION

Letters of notification were sent to 2907 patients who were operated on by the gynecologist between July 1, 1993, and March 15, 2000. Of these women, 2285 (78.6%) were counseled and tested for markers of HCV infection; 320 (11.0%) did not respond to the mailing; 26 (0.9%) replied but declined testing; 243 (8.4%) letters were undeliverable and current mailing addresses could not be obtained from the registration offices; and 33 (1.1%) women had already died when the retrospective investigation was initiated. None of them died as a result of liver disease. The mean age of the 2285 patients who agreed to HCV testing was 40 years (range, 17-90 years) when the retrospective study started in July 2000. The HCV-infected gynecologist performed 2338 gynecological and obstetric operations on these women. Regarding the patients’ risk of exposure to HCV, 488 (20.9%) of the procedures belonged to the high-risk category and 1850 (79.1%) to the medium- and low-risk groups, respectively (Table 1).

<table>
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<th>Table 1. Gynecological and Obstetric Operations Performed by the HCV-Infected Surgeon According to Patients’ Risk of Exposure*</th>
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<td><strong>Risk of Exposure</strong></td>
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*HCV indicates hepatitis C virus.

Serum samples of 7 patients were repeatedly positive for antibodies against HCV in both enzyme-linked immunosorbent assay and confirmatory immunoblot assay. The characteristics of these 7 HCV-infected women are listed in Table 2. Patients 1, 2, 4, 5, and 7 received blood transfusions before 1991 when a mandatory donor screening for antibodies against HCV was implemented in Germany. Patient 3 underwent tattooing 25 years ago. No risk factor for HCV acquisition could be established for patient 6. Patients 2 and 6 were already known to be positive for HCV, whereas the infections of the remaining 5 women were first diagnosed during the retrospective investigation. Patients 1 to 5 were viremic. Nucleotide sequencing of an HCV core fragment and subsequent phylogenetic analysis with bootstrap resampling indicated that the HCV isolates of patients 3, 4, and 5 belonged to subtype 1a. Therefore, these women did not acquire HCV from the gynecologist, who was infected with subtype 1b. Patients 1 and 2 carried the same HCV subtype as the gynecologist. The genetic distances between the partial core sequences of their and the surgeon’s HCV strains were 0.03 and 0.04, respectively, which was 10 times more than between the surgeon and the index patient infected by him during the cesarean section. The HCV 1b core sequences of patients 1 and 2 and the gynecologist were also clearly separated in phylogenetic analysis (Figure 1), and the notion that the HCV isolates of these 2 women were different from that found in the surgeon and the index patient was further sustained by sequencing of the HVR 1 of the HCV genome: the surgeon’s and the index patient’s HCV isolates were characterized by a kind of molecular fingerprint, since the HVR 1 was preceded by an unique insertion of 12 nucleotides, which was absent in all other HCV 1b sequences analyzed. A comparison of the surgeon’s and index patient’s sequences with those of patients 1 and 2 furthermore resulted in a nucleotide homology of only 54% and 65%, respectively (Figure 2). The serum samples of patients 6 and 7 were repeatedly negative in PCR analysis, indicating that these women had resolved the infection. Serotyping revealed the former presence of HCV types 3 and 1.
Specimens from an additional 4 patients were reactive in enzyme-linked immunosorbent assay but showed indeterminate and negative results in immunoblot and HCV PCR analysis, respectively. Follow-up testing after 3 and 6 months confirmed the initial findings in all 4 cases and failed to detect HCV seroconversion or viremia. All antibody-negative samples obtained from the 76 patients who still could have been in the incubation stage of acute HCV infection and from those 22 individuals receiving immunosuppressive treatment were nonreactive in nucleic acid amplification.

Taken together, the results of our virological and molecular analyses showed that besides the index patient no further women were intraoperatively infected with HCV by the gynecologist during almost 7 years. The overall HCV transmission rate was therefore 0.04% (1 per 2286, including the index patient; 95% confidence interval, 0.008%-0.25%).

### COSTS

The total direct and indirect economic costs of this retrospective investigation were approximately $120,000, including $60,000 of fixed salary for the hospital and laboratory personnel. Expenses for setting up a toll-free telephone line operated by a call center accounted for $30,000, HCV testing and molecular analyses for $20,000, and postage as well as different supplies for $10,000.

### COMMENT

During recent years, considerations about the possible public health implications of HCV transmissions from infected health care providers to susceptible patients gained some support from published case reports. To our knowledge, the retrospective investigation presented here is the most comprehensive attempt undertaken so far to determine the risk of such iatrogenic HCV transmissions. Almost 2300 women who had been previously operated on within 7 years by an HCV-infected gynecologist were tested for HCV infection. The retrospective investigation was justified because it was proven that the gynecologist had transmitted the virus to a patient during a cesarean section. The crucial differentiation between HCV transmissions caused by the gynecologist and infections contracted from other, epidemiologically unlinked sources was unequivocally achieved by nucleotide sequencing and phylogenetic analysis that are nowadays regarded as essential tools in all molecular investigations.
Hepatitis C virus (HCV) transmission from infected cardiothoracic and gynecologic surgeons therefore might be largely attributable to the distinct spectra of invasive procedures performed. This notion is further supported by the results of retrospective investigations of the risk of provider-to-patient transmission of another blood-borne pathogen, hepatitis B virus. Whereas transmission rates in outbreaks associated with cardiothoracic surgeons ranged from 5% to 17%, the risk of transmitting the virus during gynecological and obstetric operations was considerably lower (0.9% to 8.5%).

Hepatitis B virus infections in gynecology and obstetrics
almost exclusively occurring during deep pelvic surgery, especially hysterectomies, or, as in our case, cesarean sections.22,34-42 most probably reflecting the high risk of percutaneous injuries when sharp instruments are often guided by the surgeon’s finger during these procedures.44

To achieve an ultimately acceptable description of the existing risk, our finding demonstrating that the rate of HCV provider-to-patient transmission is rather low has to be supplemented, therefore, by further carefully conducted retrospective exercises that include a broad spectrum of exposure-prone procedures from different surgical specialties. Such retrospective investigations, however, are costly, involve the diversion of large monetary and staff resources, and are very likely to cause substantial anxiety among patients.14 As a result of our experience, we believe that retrospective investigations are only justified when an HCV transmission to a patient is proven or there is convincing evidence of egregious violations of standard infection-control procedures. In the aggregate, the results of our and other forthcoming retrospective studies will finally form a reliable basis for future recommendations on the management of health care workers infected with HCV.

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REFERENCES

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REFERENCES


Correction

Error in Figure 2. In the Original Investigation by Ross et al titled “Risk of Hepatitis C Virus Transmission From an Infected Gynecologist to Patients: Results of a 7-Year Retrospective Investigation” published in the April 8 issue of the ARCHIVES (2002;162:805-810), an error occurred in Figure 2 on page 809. The last line in the figure was inadvertently dropped. The corrected figure appears below. The journal regrets the error.

Figure 2. Alignment of hepatitis C virus (HCV) subtype 1b hypervariable region 1 (HVR 1) sequences and flanking regions from the gynecologist, the index patient infected by him, patients 1 and 2 identified during the retrospective investigation, and selected controls (C 1, C 2, M58335, and X61596). The HVR 1 is indicated by underscore.