Maternal and Fetal Outcomes in Pregnant Women with Acute Hepatitis E Virus Infection

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Background: Hepatitis E virus (HEV) infection is known to cause severe liver disease in pregnant women. It is unclear whether obstetric and fetal outcomes are worse in pregnant women with HEV infection than in women with other forms of viral hepatitis.

Objective: To compare maternal, obstetric, and fetal outcomes in pregnant women with acute viral hepatitis caused by HEV and other hepatitis viruses.

Design: Observational cohort.

Setting: Tertiary care hospital, New Delhi, India.

Patients: 220 consecutive pregnant women presenting with jaundice caused by acute viral hepatitis.

Measurements: Maternal mortality and medical complications, obstetric complications, deliveries, and fetal outcomes.

Results: Infection with HEV caused acute viral hepatitis in 60% of included women. Fulminant hepatic failure was more common (relative risk, 2.7 [95% CI, 1.7 to 4.2]; $P = 0.001$) and maternal mortality was greater (relative risk, 6.0 [CI, 2.7 to 13.3]; $P < 0.001$) in HEV-infected women than in non–HEV-infected women. Women with HEV infection were more likely than those with other forms of viral hepatitis to have obstetric complications (relative risk, 4.1 [CI, 1.7 to 10.2] for antepartum hemorrhage and 1.9 [CI, 1.3 to 2.7] for intrauterine fetal death; $P < 0.001$ for both) and poor fetal outcomes (relative risk, 1.2 [CI, 1.0 to 1.4] for preterm delivery [$P = 0.005$] and 1.8 [CI, 1.2 to 2.5] for stillbirth [$P = 0.026$]).

Limitations: The findings may not apply to community settings, to women who are asymptomatic or have only minor symptoms, or in the setting of an HEV epidemic.

Conclusions: Pregnant women with jaundice and acute viral hepatitis caused by HEV infection had a higher maternal mortality rate and worse obstetric and fetal outcomes than did pregnant women with jaundice and acute viral hepatitis caused by other types of viral hepatitis.

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Hepatitis E virus (HEV) is a single-stranded RNA virus that causes large-scale epidemics and sporadic cases of acute viral hepatitis in developing countries (1, 2). Infection with HEV also poses a significant risk for acute viral hepatitis to travelers in endemic areas (3). The main source of transmission of HEV is contaminated drinking water (4, 5). In men and nonpregnant women, the disease is usually self-limited and has a low case-fatality rate (<0.1%) (6). However in pregnant women, HEV infection is more severe, often leading to fulminant hepatic failure and death in up to 15% to 20% of cases. This high mortality rate was first reported in an epidemic setting in the early 1980s (7) and was reported again in a sporadic setting in 2003 (8).

Information is limited and conflicting on the effect of HEV infection on maternal, obstetric, and fetal outcomes (9, 10). Therefore, we describe the prevalence and clinical outcomes of acute viral hepatitis in a series of HEV-infected pregnant women and compare their maternal, obstetric, and fetal outcomes with those of pregnant women without HEV infection.

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METHODS

Setting and Participants

The study was conducted at the Department of Obstetrics and Gynecology, Lady Hardinge Medical College, and Shrimati Sucheta Kriplani Hospital, New Delhi, India (a large tertiary care hospital), in collaboration with the Department of Gastroenterology, G.B. Pant Hospital, New Delhi. Consecutive pregnant women at any gestational stage who presented between January 2003 and July 2005 with acute viral hepatitis were systematically assessed for hepatitis virus infection by using liver function tests and serologic analysis. Acute viral hepatitis was diagnosed (7) by a serum bilirubin level of 34 μmol/L or greater (≥2 mg/dL); a serum alanine aminotransferase level 2.5 times the upper limit of normal or greater; and positivity for any hepatotropic virus by using the following serologic tests: hepatitis B surface antigen; antibody to hepatitis C virus; and IgM antibodies to hepatitis A virus, hepatitis B core antigen, hepatitis delta virus, and HEV. We excluded patients with negative results on viral serologic examination, those with dual viral infection, those with clinical evidence of other causes of jaundice (such as biliary obstruction, the HELLP syndrome [hemolytic anemia, elevated liver enzyme level, low platelet count], acute fatty liver of pregnancy, hemolytic jaundice, and drug-induced jaundice),

and those with clinical or laboratory evidence of chronic liver disease.

Women who met the case definition of acute viral hepatitis were managed in a separate hepatitis hospital ward. Management depended on whether the patient's acute viral hepatitis was complicated by fulminant hepatic failure, which was diagnosed when hepatic encephalopathy developed in a patient with acute viral hepatitis within 4 weeks of the onset of jaundice (11).

Patients without fulminant hepatic failure were given standard care and were monitored for signs and complications of acute viral hepatitis (fever, edema, ascites, paralytic ileus, nasal and gastrointestinal hemorrhage, high leukocyte count, high creatinine concentration, hepatic encephalopathy, clinically significant coagulation defect [international normalized ratio > 2.0], hypoglycemia, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, and hypocalcemia), and obstetric complications (antepartum, intrapartum, or postpartum hemorrhage; premature rupture of membranes; and intrauterine death). If their condition improved, patients were discharged and instructed to return for regular outpatient follow-up visits until delivery.

Patients with fulminant hepatic failure were managed with supportive care in the intensive care unit because liver transplantation facilities are not available in the hospital. They were monitored for increased intracranial tension along with other medical and obstetric complications. They received 20% mannitol, lactulose, antibiotics, parenteral nutrition, and ventilatory support, as needed. Women without fulminant hepatic failure who had fetal distress, meconium staining of amniotic fluid, no progress of labor, or obstructed labor underwent cesarian section. Termination of pregnancy was considered in cases of intrauterine death, severe intrauterine growth retardation, a nonreactive non–stress test result, postdated pregnancy, and premature rupture of membrane at term only if the patient had improving liver function and a coagulation profile that could be further corrected by giving fresh frozen plasma. Termination of pregnancy was not considered for women with fulminant hepatic failure. All women with manifestations of bleeding were infused with fresh frozen plasma and packed red cells.

In keeping with the policy of our institutions, the study did not require institutional review board approval or documented informed consent from patients for study participation because patients received care according to a standard clinical protocol, their care was not influenced by their inclusion in the study, and data were collected and recorded according to ethical standards and norms in India and were analyzed with total anonymity of patients.

Statistical Analysis

We used the *t* test and the Mann–Whitney U test to compare normally distributed data and non-normally distributed data, respectively, of HEV-infected and non–HEV-infected patients. The chi-square test was used to compare discrete values between groups. A *P* value less than 0.05 was considered significant. Relative risk was calculated for all complications in HEV-infected pregnant women versus non–HEV-infected pregnant women. Statistical analyses were done by using SPSS, version 13.0 (SPSS, Chicago, Illinois).

Role of the Funding Source

The study received no external funding.

Context

Hepatitis E virus (HEV) infection causes severe liver disease in pregnant women.

Contribution

In a case series of 220 pregnant women with jaundice and acute viral hepatitis, the authors observed that women with HEV infection more often died and had more obstetric complications and worse fetal outcomes than did women with other forms of viral hepatitis.

Caution

The series was restricted to symptomatic women at a referral center.

Implication

Infection with HEV not only causes more severe liver disease in pregnant women but also appears to contribute to worse obstetric and fetal outcomes compared with other forms of viral hepatitis.

—The Editors

RESULTS

Patients

Of the 33 385 pregnant women who were admitted during the study period, 316 (0.9%) presented with jaundice. Ninety-two were excluded for causes of jaundice other than viral hepatitis (intrahepatic cholestasis of pregnancy [41 women], the HELLP syndrome [6 women], acute fatty liver of pregnancy [3 women], drug hepatotoxicity [7 women], hemolytic jaundice [14 women], choledocholithiasis [6 women], and unknown cause [15 women]), and 4 were excluded for dual viral infection. The remaining 220 pregnant women with jaundice met the inclusion criteria for acute viral hepatitis. None had evidence of autoimmune disease.

Table 1 shows patient characteristics. The mean maternal age was 22.4 years (SD, 3.2). Sixty-one women (28%) were in the second trimester of pregnancy (mean gestational age, 26.2 weeks [SD, 2.0]) and 159 (72%) were in the third trimester (mean gestational age, 34.2 weeks [SD, 2.6]). The mean duration of jaundice before hospitalization was 4.9 days (SD, 2).

Table 1. **Patient Characteristics***

Variable	HEV-Infected Women ($n = 132$)	Non–HEV-Infected Women ($n = 88$)	*P* Value
Mean age (SD), *y*	22.2 (3.4)	22.5 (3.0)	0.54
Median gravida (range), *n*	2 (1–6)	2 (1–7)	0.96
Mean gestational age (SD), *wk*	31 (4.1)	33 (4.4)	0.004
Trimester, *n (%)*			0.023
Second	44 (33)	17 (19)	
Third	88 (67)	71 (81)	
Socioeconomic status, *n (%)*†			0.29
Middle	58 (44)	45 (51)	
Low	74 (56)	43 (49)	
Median duration of jaundice before admission (range), *d*	4 (1–15)	4.5 (2–10)	0.68
Acute viral hepatitis, *n (%)*			<0.001
With fulminant hepatic failure	73 (55)	18 (20)	
Without fulminant hepatic failure	59 (45)	70 (80)	
Laboratory data			
Mean hemoglobin level (SD), *g/L*	84 (14)	88 (12)	0.026
Median leukocyte count (range), *cells* $\times 10^9$*/L*	12 (4–33)	9.5 (4–28)	<0.001
Mean platelet count (SD), *cells* $\times 10^9$*/L*	211.3 (59.6)	238.2 (56.4)	0.001
Mean serum bilirubin level (SD)			<0.001
μmol/L	255.0 (90.1)	181.9 (86.7)	
mg/dL	15.0 (5.3)	10.7 (5.1)	
Median alanine aminotransferase level (range), *U/L*	90.5 (24.8–310.1)	54.5 (10.0–212.2)	0.001
Median prothrombin time (range), *s*‡	58 (15–150)	19 (15–105)	0.001
Median international normalized ratio (range)	4.0 (1.0–18.6)	1.6 (1.0–7.1)	0.001
Mean serum albumin level (SD), *g/L*	36 (10)	42 (9)	<0.001

* HEV = hepatitis E virus.
† Based on reference 12.
‡ Control value, 15 seconds.

Cause of Hepatitis

Infection with HEV was the most common cause of acute viral hepatitis (132 participants [60%]) (**Table 1**). Hepatitis B virus (HBV) infection was the most common cause of non–HEV acute viral hepatitis (72 participants [33%]). Fewer HEV-infected patients than non–HEV-infected patients were in their third trimester of pregnancy, corresponding to a lower mean gestational age for HEV-infected patients (31 weeks [SD, 4.1] vs. 33 weeks [SD, 4.4]; $P = 0.004$) (**Table 1**). The median duration of jaundice did not differ between HEV-infected women and non–HEV-infected women (4 days [range, 1 to 15 days] vs. 4.5 days [range, 2 to 10 days]; $P = 0.68$).

Fulminant Hepatic Failure

Ninety-one women (41%) had fulminant hepatic failure, of whom 54 (59%) had fulminant hepatic failure on admission and 37 (41%) developed fulminant hepatic failure during hospitalization. Fulminant hepatic failure was more common among HEV-infected women than non–HEV-infected women (73 of 132 [55%] vs. 18 of 88 [20%]; relative risk, 2.7 [CI, 1.7 to 4.2]; $P < 0.001$) (**Table 1**) and among HEV-infected women in their third trimester (46 of 88 [52%] vs. 11 of 71 [15%] noninfected women; relative risk, 3.4 [CI, 1.9 to 6.0]; $P < 0.001$). The frequency of fulminant hepatic failure did not statistically significantly differ between HEV-infected women and non–HEV-infected women in their second trimester (27 of 44 [61%] vs. 7 of 17 [41%]; $P = 0.26$).

Jaundice before hospital admission was of longer duration in women with fulminant hepatic failure than in those without fulminant hepatic failure (5.4 days [SD, 2.6] vs. 4.6 days [SD, 1.5]; $P = 0.010$). In women who developed fulminant hepatic failure, the mean interval from onset of jaundice to onset of encephalopathy was 108 hours (SD, 58) and was similar in HEV-infected and non–HEV-infected women (112 hours [SD, 60] vs. 93 hours [SD, 50]; $P = 0.18$). The mean duration of encephalopathy before admission was 20 hours (SD, 15) and was similar in HEV-infected and non–HEV-infected women.

Maternal Mortality and Complications of Infection

Maternal mortality was higher in HEV-infected women and occurred exclusively in women with fulminant hepatic failure (**Table 2**). Signs and complications of infection that differed by HEV status were an international normalized ratio greater than 2.0, nasal or gastrointestinal hemorrhage, leukocyte count of 11×10^9 cells/L or greater, high serum creatinine concentration ($\geq$34 μmol/L [$\geq$2 mg/dL]), ascites, and signs of increased intracranial tension. Differences between groups in other clinical and laboratory features, and complications did not reach statistical significance (data not shown).

Obstetric Complications

Antepartum hemorrhage and intrauterine fetal death were more frequent in HEV-infected women than in non–HEV infected women, whereas rates of postpartum hemorrhage and premature rupture of membranes did not differ between groups (**Table 3**).

Deliveries

The median interval between admission and delivery was 24 hours (range, 1 to 312 hours) in HEV-infected women and 18 hours (range, 6 to 168 hours) in non–HEV-infected women ($P < 0.01$). Of 186 deliveries, 89 patients (41%) were in labor at the time of admission and 97 (44%) went into labor after admission; 156 deliveries (84%) were preterm (gestational age <37 weeks) and 30 (16%) were full term (gestational age ≥37 weeks). Preterm deliveries were more common in HEV-infected women, and full-term deliveries were more common in non–HEV-infected women. Seven women had cesarean section. No patient with fulminant hepatic failure was induced.

Of the 34 women (15%) who did not deliver while hospitalized, 14 were discharged uneventfully and gave birth to healthy babies. The remaining 20 women died in the hospital before delivery; 19 of these women had HEV infection (**Table 3**).

Fetal Outcomes

Pregnant women who were infected with HEV had fewer live births and more stillbirths than non–HEV-infected women (**Table 3**). The number of spontaneous abortions or neonatal deaths did not differ between the groups. Of 30 neonatal deaths, 28 (93%) were preterm, and 17 of the 28 preterm deaths (61%) occurred in HEV-infected women.

Seventy women with fulminant hepatic failure and 116 women without fulminant hepatic failure delivered. Only 2 of the 70 deliveries (3%) in women with fulminant hepatic failure were live births (2 of 53 deliveries [4%] in HEV-infected women vs. 0 of 17 deliveries [0%] in non–HEV-infected women; $P = 1.0$). Both women with fulminant hepatic failure who had live births were infected with HEV. One child survived and 1 died (neonatal death).

Of the 116 deliveries in women without fulminant hepatic failure, significantly fewer live births were among HEV-infected women than non–HEV-infected women (20 of 52 [38%] vs. 40 of 64 [62%]; $P = 0.009$). Among the 28 women without fulminant hepatic failure who delivered live babies at full term, live births were less common in HEV-infected women than non–HEV-infected women (5 of 8 [62%] vs. 19 of 20 [95%]; $P = 0.026$).

DISCUSSION

In this prospective study of 33 385 pregnant women admitted to a New Delhi hospital, we found that 220 (0.6%) had jaundice caused by acute viral hepatitis and that HEV infection accounted for 60% of these cases. Fulminant hepatic failure was more common in HEV-infected women, and more HEV-infected women died, had obstetric complications, or had worse fetal outcomes than did women who had jaundice and acute viral hepatitis caused by other hepatitis viruses.

The **Appendix Table** (available at www.annals.org) summarizes results of other studies. Our observation that HEV infection causes 60% of cases of jaundice and acute viral hepatitis among pregnant women is consistent with those of 2 other studies. Jaiswal and colleagues (13) in central India and Aziz and associates (14) in Pakistan reported that HEV is responsible for 58% and 62% of cases of acute viral hepatitis in pregnant women, respectively. Two studies from New Delhi (15, 16) reported slightly lower prevalences (45% and 37%), and a study of sporadic HEV infection in the context of multiple HEV epidemics in Kashmir reported a prevalence of 86% among pregnant patients with acute viral hepatitis (8). These differences in estimates may be due to the small samples and regional differences in HEV prevalence.

Our observation that a high proportion of HEV-infected pregnant women develop fulminant hepatic failure has been previously recognized. In a 1981 report of epidemic HEV infection, 22% of pregnant women with acute viral hepatitis developed fulminant hepatic failure, compared with 0% of nonpregnant women and 2.8% of

Table 2. **Maternal Mortality and Medical Complications***

Variable	HEV-Infected Women ($n = 132$), n/n (%)	Non–HEV-Infected Women ($n = 88$), n/n (%)	Relative Risk (95% CI)	*P* Value
Maternal mortality rate				
Overall	54/132 (41)	6/88 (7)	6.0 (2.7–13.3)	<0.001
Patients with fulminant hepatic failure	54/73 (74)	6/18 (33)	2.2 (1.1–4.3)	0.001
Second trimester	18/27 (66)	0/7 (0)	–	0.002
Third trimester	36/46 (78)	6/11 (54)	1.4 (0.8–2.5)	0.11
Patients without fulminant hepatic failure	0/59 (0)	0/70 (0)	–	1.00
Medical complications				
Coagulation defect†	104/132 (79)	32/88 (36)	2.2 (1.6–2.9)	<0.001
Nasal or gastrointestinal hemorrhage	25/132 (19)	4/88 (4)	4.2 (1.5–11.6)	0.002
Leukocyte count ≥11 × 10^9 cells/L	86/132 (65)	31/88 (35)	1.8 (1.4–2.5)	<0.001
Serum creatinine concentration ≥34 μmol/L (≥2 mg/dL)	39/132 (30)	4/88 (4)	6.5 (2.4–17.5)	<0.001
Ascites	33/132 (25)	5/88 (6)	4.4 (1.8–10.8)	<0.001
Clinical signs of increased intracranial tension	27/132 (20)	1/88 (1)	18.0 (2.5–130.1)	<0.001

* HEV = hepatitis E virus.
† International normalized ratio >2.0.

Table 3. **Obstetric Complications and Fetal Outcomes***

Variable	HEV-Infected Women (*n* = 132), *n/n* (%)	Non–HEV-Infected Women (*n* = 88), *n/n* (%)	Relative Risk (95% CI)	*P* Value
Obstetric complications				
Antepartum hemorrhage	31/132 (23)	5/88 (6)	4.1 (1.7–10.2)	<0.001
Second trimester	15/44 (34)	0/17 (0)	–	0.006
Third trimester	16/88 (18)	5/71 (7)	2.6 (1.0–6.7)	0.039
Postpartum hemorrhage	18/132 (14)	8/88 (9)	1.5 (0.7–3.3)	0.31
Second trimester	5/44 (11)	2/17 (12)	1.0 (0.2–4.5)	0.96
Third trimester	13/88 (15)	6/71 (8)	1.7 (0.7–4.4)	0.22
Premature rupture of membranes	12/132 (9)	3/88 (3)	2.7 (0.8–9.2)	0.10
Second trimester	5/44 (11)	0/17 (0)	–	0.15
Third trimester	7/88 (8)	3/71 (4)	1.9 (0.5–7.0)	0.34
Intrauterine fetal deaths	77/132 (58)	27/88 (31)	1.9 (1.3–2.7)	<0.001
Second trimester	33/44 (75)	10/17 (59)	1.3 (0.8–2.0)	0.21
Third trimester	44/88 (50)	17/71 (24)	2.1 (1.3–3.3)	0.001
Fetal outcomes†				
Preterm delivery	95/105 (90)	61/81 (75)	1.2 (1.0–1.4)	0.005
Poor fetal outcome	83/105 (79)	41/81 (51)	1.6 (1.2–2.0)	<0.001
Second trimester	33/33 (100)	14/15 (93)	–	0.68
Third trimester	50/72 (69)	27/66 (41)	1.7 (1.2–2.4)	0.001
Spontaneous abortions	8/105 (8)	4/81 (3)	1.5 (0.5–4.9)	0.68
Stillbirths	57/105 (54)	25/81 (1)	1.8 (1.2–2.5)	0.026
Neonatal deaths	18/105 (17)	12/81 (15)	1.2 (0.6–2.3)	1.00
Live births (in hospital)	22/105 (21)	40/81 (49)	0.4 (0.3–0.6)	<0.001
Second trimester	0/33 (0)	1/15 (7)	–	0.68
Third trimester	22/72 (31)	39/66 (59)	0.5 (0.3–0.8)	0.001
Other maternal outcomes				
Recovered and discharged from hospital before delivery and had live birth on follow-up	8/132 (6)	6/88 (7)	0.9 (0.3–2.5)	0.82
Died in hospital before delivery	19/132 (14)	1/88 (1)	12.7 (1.7–92.9)	0.001

* HEV = hepatitis E virus.
† Among 186 deliveries. The few fetal losses that occurred during delivery are counted as stillbirths, not as intrauterine fetal deaths.

men (7). Other studies documented the development of fulminant hepatic failure in 32% to 69% of HEV-infected pregnant women with acute viral hepatitis in sporadic settings (8, 13, 15, 16).

The reasons for the high frequency of fulminant hepatic failure are unclear and are being researched. A shift in T_H1–T_H2 balance toward a T_H2 response in pregnant women with HEV infection but not in nonpregnant women with HEV infection (17) may point toward a primary immunologic cause of severe disease in pregnancy. In addition, hormones of pregnancy, especially estrogen and progesterone, might impair cellular immunity by triggering adapter protein (ORF3 of HEV), which could facilitate viral replication and lead to release of cytokines and liver cell apoptosis (18, 19).

Obstetric and fetal outcomes in pregnant women with acute viral hepatitis have not been adequately studied. Of 186 deliveries in our study, 84% were preterm, and a significantly higher proportion of preterm deliveries occurred in HEV-infected women. Only 1 study reported a high frequency of preterm delivery in HEV-infected pregnant women (67%) (15).

To our knowledge, our observation that HEV-infected pregnant women had worse fetal outcomes has not been previously reported. The mechanism underlying these outcomes is not known, but vertical transmission might be a cause. In 1 study, vertical transmission of HEV was detected in 5 newborns whose mothers had developed hepatitis during an epidemic of waterborne HEV infection (20). Vertical transmission was also detected in 26 cases of HEV RNA–positive women by testing for HEV RNA in cord blood or newborn blood (21), although the possibility of contamination of cord blood with the maternal blood could not be excluded.

Our study has several limitations. Our hospital is a tertiary care center, and the relatively high frequency of acute viral hepatitis in pregnancy and of fulminant hepatic failure in women with acute viral hepatitis might be explained in part by referral bias. In addition, the fact that many women with HBV hepatitis are referred to our hospital in their third trimester for HBV immunoglobulin therapy may influence comparisons between HEV-infected women and non–HEV-infected women, because HBV-infected women form a major portion of non–HEV-infected groups. However, our findings for non–HEV-infected women are consistent with those of other studies from the region (13, 14, 16). In addition, whether cases of HBV hepatitis were due to acute HBV infection or reactivation of chronic HBV infection in pregnancy remains to be determined. We studied hospitalized women who presented with symptoms and signs of acute viral hepatitis. Thus, our findings do not apply to the many patients who were asymptomatic or had only minor symptoms and were seen as outpatients. Our observations were made in the

setting of sporadic transmission of HEV and cannot be generalized to an epidemic setting. Our data may have limited applicability in settings in which orthotopic liver transplantation is readily accessible, although availability of the procedure would be unlikely to alter obstetric or fetal outcomes.

In summary, in a prospective series of 220 pregnant women with jaundice and acute viral hepatitis, HEV infection caused 60% of cases and was associated with an increase in maternal mortality, obstetric complications, and poor fetal outcomes. Further research is warranted to determine how best to prevent these adverse outcomes.

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Appendix Table. **Studies of Hepatitis E Virus Infection in Pregnancy**

Study, Year (Reference)	Patients, *n*	Prevalence of Hepatitis E Virus Infection, %	Patients with Fulminant Hepatic Failure, %	Mortality Rate, %
Medhat et al., 1993 (22)	55	30	43	100
Tsega et al., 1993 (23)	32	59	–	42
Jaiswal et al., 2001 (13)	127	58	58	45
Singh et al., 2003 (16)	60	37	64	64
Khuroo and Kamili, 2003 (8)	76	86	69	55
Strand et al., 2003 (24)	20	40	–	30
Kumar et al., 2004 (15)	65	45	32	73
Present study, 2007	220	60	55	41