Screening for hepatitis C virus infection in methadone-maintained mothers and their infants

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ABSTRACT

Objective: To describe the patterns of screening for hepatitis C virus (HCV) infection in methadone-maintained pregnant women and their infants.

Design, setting and patients: Retrospective review of medical records from one rural and two metropolitan hospitals in New South Wales for pregnant women on methadone maintenance treatment and infants born to these women between 1 January 2000 and 31 December 2006, as well as records for pregnant women who were not on methadone treatment.

Main outcome measures: Rates of anti-HCV antibody and HCV RNA testing for pregnant women and their infants, and ages at which infants attended follow-up appointments.

Results: Of 295 pregnant women on methadone maintenance treatment, 288 were tested for anti-HCV antibodies (98%), compared with 1995 of 9987 women who were not on methadone treatment (20%) ($P < 0.001$). Seropositive results were obtained for 243 women in the methadone group (84%) and 54 in the non-methadone group (3%) ($P < 0.001$), of whom 44 (18%) and 17 (31%), respectively, were subsequently tested for HCV RNA ($P = 0.03$). HCV RNA test results were positive for 31 (70%) and 10 (59%) seropositive women in the methadone and non-methadone groups, respectively ($P = 0.39$). Of infants of HCV-seropositive methadone-maintained mothers, 27% of those for whom we had follow-up attendance data received HCV screening, and one of these infants tested positive for anti-HCV antibodies and HCV RNA.

Conclusions: Screening for HCV infection in the high-risk population of pregnant women on methadone maintenance treatment and their infants is inadequate. This could lead to significant underdetection of active HCV infection in this high-risk population, and their infants. Current screening guidelines may therefore need to be revised.

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Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, including cirrhosis and liver cancer. It is estimated that about 3% of the world's population is infected with HCV.[1] In Australia, it is estimated that 264 000 people were seropositive for HCV in 2005.[2] Transmission of HCV in Australia occurs mainly through intravenous drug use. Depending on factors such as duration of injecting, age and sex, the proportion of intravenous drug users who are seropositive for HCV has been estimated to be 50%–75%.[3-5]

Mother-to-infant transmission, or vertical transmission, of HCV occurs infrequently,[6] but is a cause for concern. This is because of possible chronic HCV infection and progression to cirrhosis and hepatocellular carcinoma later in life, as well as occasional development of end-stage liver disease in childhood.[7]

Vertical transmission of HCV occurs only when the mother is HCV RNA-positive (ie, viraemic) at the time of birth, with the risk of transmission being 5%–10%.[8-10] After transmission, persistent infection develops in at least 85% of infected newborns, even in the absence of biochemical evidence of liver disease.[11,12]

Screening for HCV infection in the antenatal care setting has been deemed to be important for detecting infection in mothers and identifying infants who are most at risk of vertical transmission. The current NSW Department of Health guidelines recommend that HCV screening be performed for women with risk factors such as a history of intravenous drug use,[13] while the current Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) guidelines recommend universal screening of pregnant women regardless of the presence of risk factors.[14]

The NSW Department of Health and RANZCOG guidelines both recommend that women who are seropositive for HCV be tested by HCV RNA polymerase chain reaction (PCR) to detect viraemia, and that infants of women who test positive for HCV RNA be screened for HCV by serological testing at 18 months of age.[13,14] Whether these recommendations are being followed in practice is unknown. The aim of this study was to describe the patterns of HCV screening in pregnant women on methadone maintenance treatment and their infants.

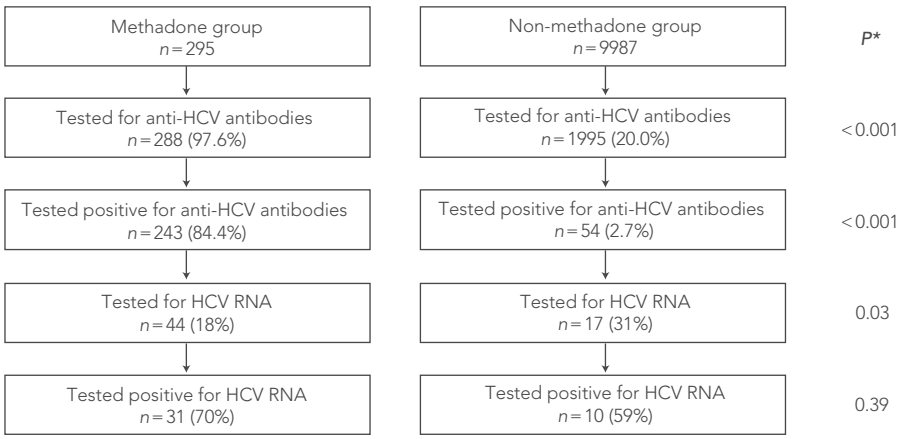
METHODS

We undertook a retrospective review of electronic and paper medical records from two major metropolitan hospitals (in Penrith and Blacktown) that belong to the Sydney West Area Health Service and one rural hospital in New South Wales. These hospitals have a combined annual birth rate of more than 7500.

The two metropolitan hospitals have strong clinical links, which facilitated the ethics approval process and data collection. The proportion of pregnant woman who use illicit drugs in pregnancy is very high in the area serviced by these hospitals (approximately 80 pregnant mothers per year, accounting for about 1% of births, according to personal experience of local clinicians); this enabled us to acquire data for a reasonable sample size. According to Australian Bureau of Statistics data, Socio-Economic Indexes for Areas scores for Penrith and Blacktown in 2006 were in the lower deciles.[15] Aboriginal and Torres Strait Islanders represented 2.5% of the population in the Penrith local government area[16] and 2.7% of the population in the Blacktown local government area,[17] compared with 2.2% in NSW overall.[18]

The rural hospital was selected because of close clinical and academic ties with one of the metropolitan hospitals, which facilitated the ethics approval process and data collection. The population of pregnant women who use illicit drugs in pregnancy in the area serviced by this hospital was also large (approximately 30 pregnant women per year, according to personal experience of local clinicians).

1 Maternal hepatitis C virus (HCV) screening undertaken for pregnant women on methadone maintenance treatment, and those not on methadone treatment



* *P* values represent differences between methadone and non-methadone groups. ◆

Inclusion criteria were pregnant women on methadone maintenance treatment for opiate dependence who gave birth to live infant/s between 1 January 2000 and 31 December 2006. Eligible mother–infant dyads were identified using the local obstetric database and confirmed by the *International statistical classification of diseases and related health problems*, 10th revision, Australian modification coding for: antenatal drug dependence with delivery (F11.2); antenatal drug withdrawal with delivery (F11.3); neonatal withdrawal symptoms from maternal drug use (P96.1); and fetus and newborn affected by maternal drug use (P04.4). The local obstetric database was also used to identify pregnant women not on methadone maintenance treatment who gave birth at the larger of the two metropolitan hospitals between 1 January 2004 and 31 December 2006.

Data obtained included all available maternal and infant anti-HCV antibody and HCV RNA test results. The larger metropolitan hospital had a specialised follow-up clinic for infants up to 3 years of age. Follow-up of infants born at the other hospitals usually involved local general practitioners and paediatricians, making data collection difficult. Follow-up attendance data for infants born to HCV-seropositive mothers was thus obtained from the larger metropolitan hospital only. Follow-up of HCV-seropositive women not on methadone maintenance treatment and their infants (the control group) was the responsibility of the obstetrician and local GP.

The larger metropolitan hospital also had a Drugs in Pregnancy Service, staffed by a multidisciplinary medical and social case-management team of obstetricians, physicians, nurses, drug and alcohol counsellors, and social workers. This service provided structured follow-up for infants of methadone-maintained HCV-seropositive mothers. In cases where a follow-up appointment was missed, the social worker contacted the parents or carers. In addition, the parents or carers were notified in writing to reschedule an appointment. In many cases, contact was difficult to establish months after discharge owing to the mobile nature of the study population.

The methadone-maintained women who attended the larger metropolitan hospital received antenatal care at the Drugs in Pregnancy Service. Women not on methadone maintenance received antenatal care at the hospital service (which has its own pathology service) or from private obstetricians or GPs (who have a variety of laboratory service providers). HCV screening in this group was therefore restricted to only those who received antenatal care at the hospital service.

Ethics approval

The study was approved by the local human research ethics committees. The ethics committee of the rural hospital had a proviso to conceal its name and location for confidentiality reasons.

Statistical analysis

Statistical analysis was performed using SPSS 16.0.1 (SPSS Inc, Chicago, Ill, USA). Simple comparisons were made using the Fisher's exact test or χ^2 test for all categorical data, and the unpaired *t* test for normally distributed continuous data. Non-parametric tests were used for non-normal data. Significance was assumed at $P < 0.05$.

RESULTS

Two hundred and ninety-five pregnant women on methadone maintenance treatment were identified; they gave birth to a total of 299 infants during the study period. A group of 9987 pregnant women who were not on methadone maintenance treatment and received antenatal care at the larger metropolitan hospital were also identified. The mean ages of women in the methadone and non-methadone groups were comparable (27.6 ± 5.3 years and 27.9 ± 6.0 years, respectively).

Maternal screening

Serological testing for anti-HCV antibodies was performed for 97.6% of women in the methadone group, compared with 20.0% of women in the non-methadone group ($P < 0.001$). Of women who were seropositive for HCV, those in the methadone group were significantly younger than those in the non-methadone group (27.9 ± 5.4 years v 30.2 ± 6.1 years; $P = 0.01$). Subsequent HCV RNA testing was performed in 18.1% of HCV-seropositive women in the methadone group, compared with 31.5% of HCV-seropositive women in the non-methadone group ($P = 0.03$) (Box 1).

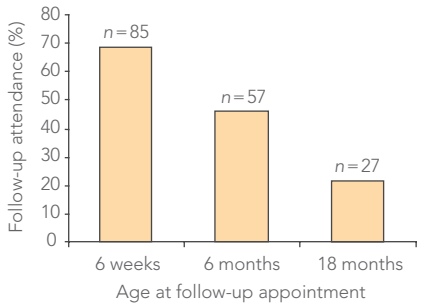
The proportion of pregnant women who were HCV seropositive in the methadone group was significantly higher than those in the non-methadone group ($P < 0.001$). However, the proportion of seropositive women who were also HCV RNA-positive was not statistically different between the two groups ($P = 0.39$).

Infant screening

Of 195 infants born to HCV-seropositive mothers at the larger metropolitan hospital, 124 were followed up at various ages (64%) (Box 2). The remainder were lost to follow-up, even though a follow-up appointment was arranged at discharge. Of those 124 infants for whom we had follow-up attendance data, 34 (27%) received some level of screening during the 18 months after birth, and positive results for anti-HCV antibodies and HCV RNA were returned for one infant at 18 months of age.

Twenty-seven of the 124 infants attended the recommended follow-up at 18 months of age (22%), of whom 19 were tested for

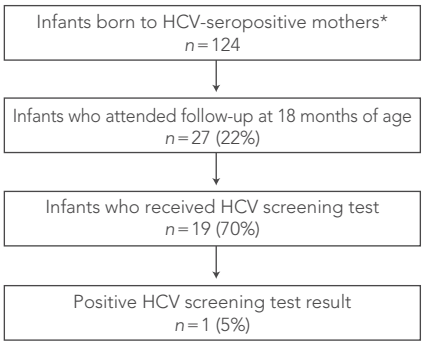
2 Follow-up appointment attendance for infants born to mothers who were on methadone maintenance treatment and were seropositive for hepatitis C virus*



* Data represent proportions calculated using the denominator of 124 infants who were born at the larger of two metropolitan hospitals for whom follow-up attendance data were available. ◆

either anti-HCV antibodies or HCV RNA (70%) (Box 3).

3 Rates of 18-month follow-up appointment attendance and rates and results of hepatitis C virus (HCV) screening tests, for infants born to HCV-seropositive mothers at a metropolitan birthing centre



* Data represent infants born at the larger of two metropolitan hospitals for whom follow-up attendance data were available; analysis across all hospitals included in the study was not possible owing to screening policies and follow-up protocols. ◆

DISCUSSION

To our knowledge, this is the first study to investigate the seroprevalence of HCV in pregnant women on methadone replacement treatment. Approximately 98% of methadone-maintained pregnant women underwent HCV serological testing, of whom 84% were seropositive. Of those who were seropositive, 18% were subsequently tested for HCV RNA, and 71% of those tested were HCV RNA-positive. This is in keeping with previously published data, which showed that up to 75% of HCV-seropositive individuals with a past history of intravenous drug use are viraemic.[19-21]

In an article published in 2003, HCV screening practice was shown to be variable — 24 of 62 Australian public hospital-based obstetric units surveyed had a specific antenatal testing policy for HCV (39%), and 14 offered universal antenatal testing for HCV (23%).[22] Our data highlight that HCV testing practice during pregnancy is inadequate, as most HCV RNA-positive mothers in our study would have missed testing. This implies that the opportunity for monitoring and future therapy in this high-risk group was lost. Awareness of an infectious maternal HCV status enables counselling and support regarding maternal therapeutic options, as well as caution in terms of preventing transmission to partners.

Inadequate screening was not limited to the methadone-maintained women; screening was also inadequate in the non-methadone group, although the follow-up RNA testing was slightly better. This implies that sociobehavioural factors in the methadone group might affect screening rates. Whatever the reason, it is clear that HCV screening in pregnancy is not adequately followed through. In addition, screening patterns and test results at the rural and metropolitan settings we studied have previously been shown to be similar.[23]

Our study also showed that about one in five infants born to HCV-seropositive mothers, of those for whom we had follow-up attendance data, attended a follow-up appointment at 18 months of age. Therefore, most infants with the highest known risk for acquiring HCV missed out on testing at the recommended age. In addition, we identified one case of HCV vertical transmission from the 295 methadone-maintained women, of whom 243 were HCV-seropositive. Assuming an approximate prevalence of 75% HCV RNA positivity among HCV-seropositive individuals[19-21] and a 5% vertical transmission rate,[8-10] we would have missed about 10 cases of vertical HCV transmission. Although the prevalence of HCV infection in children in Australia is unknown, it has been estimated that 75–100 new cases of vertically acquired HCV occur each year. The much lower reported number of cases (27 in 2003, of which 12 were confirmed[24]) implies that childhood HCV infection is underdiagnosed in Australia.[19]

Limitations of our study include its retrospective design, the small number of hospitals included, and possible underestimation of HCV testing rates for infants. However, the observation that uptake of HCV testing for infants born to HCV-seropositive mothers is poor is an important finding that is likely to be generalisable. In addition, HCV testing might have occurred in the private sector (eg, during visits to local doctors and other family and child health services). Prerequisites for this include appropriate documentation of maternal HCV status being provided to the private sector clinicians, or parents requesting HCV testing. Although such scenarios might have occurred in a few cases, we believe that this would not have affected our overall results.

4 Hepatitis C virus (HCV) screening recommendations for pregnant women and their infants

- We recommend that the development of a national HCV registry, similar to the existing National HIV Database,[25] be considered. This would enable tracking of children with HCV infection, hence a reduction of the loss to follow-up over children's lifetimes, and provide a greater understanding of the natural history and progression of HCV infection. It would also provide reliable data on which to base future recommendations.
- We reinforce the Royal Australian and New Zealand College of Obstetricians and Gynaecologists recommendation that all pregnant women be screened for HCV infection. To achieve broader implementation of this recommendation, we propose that, at the first antenatal visit, blood be collected and tested for anti-HCV antibodies, and collected and stored for RNA testing. RNA testing should only proceed for patients who are HCV seropositive. This would address non-compliance with respect to RNA testing and minimise the costs of universal RNA testing.
- In addition, we recommend that infants of HCV RNA-positive mothers be tested for HCV RNA at 6 weeks and 6 months of age, and tested for anti-HCV antibodies at 18 months of age. We justify our recommendation of testing at 6 weeks as infants are more likely to be followed up at an earlier appointment, and perinatal-acquired infection can be detected at this age. Testing at 6 months may capture data on clearance of neonatal infection — that is, identify infants with chronic or persistent infection. ◆

There are numerous advantages of HCV screening and identifying patients with HCV infection. HCV is a notifiable disease in Australia, but because most cases of vertically transmitted HCV go undetected, screening would allow the true extent of the problem to become known. It is important to identify HCV-positive children — this enables monitoring of viral activity and disease by clinicians, who might initiate treatment or advise vaccination against other viral hepatitides that may facilitate progression to liver disease.[19]

Our recommendations regarding screening for HCV infection in pregnant women and their infants, based on our findings, are shown in Box 4.

Current HCV screening practice in the high-risk group of methadone-maintained pregnant women and their infants is inadequate. Failure to identify pregnant women with HCV viraemia leads to a failure to identify infants who are most at risk of vertical transmission. A more consistent approach for maternal RNA testing is required, which may be best achieved by educating health care providers who provide antenatal care to pregnant women who are at high risk of HCV viraemia. In addition, a greater proportion of affected infants may be detected by use of the specific strategies outlined in this article. We believe that this approach to testing, particularly in the framework of a national registry, will give paediatricians an opportunity to elucidate the true incidence, natural history and prognosis of an important, but perhaps neglected, disease of childhood.

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COMPETING INTERESTS

None identified.

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