Knowledge update on screening for hepatitis C virus in pregnancy

Claire Thorne, February 2011

1. Process

A literature search was carried out by Paula Coles, information scientist, to find citations on screening for hepatitis C virus (HCV) published since the UK National Screening Committee's consideration of the topic, which was published in December 2003. The search was carried out on publications from January 2003 to September 16 2010.

Sources searched were Medline (OvidSP), Embase, Cinahl, Web of Knowledge and the Cochrane Library. Websites of relevant UK organisations were also searched for guidelines. < . A total of 3270 citations were identified initially, with a total of 2507 potentially relevant references left after removal of duplicate references. The titles and abstracts of these 2507 publications were scanned for relevance to screening for HCV in pregnancy, particularly focusing on the following NSC criteria that were not fulfilled at the time of the last review:

- **The condition**: long term natural history of vertically acquired HCV
- **The test**: the positive predictive value of current tests is low due to the low prevalence of HCV infection in the antenatal population of the UK, meaning that a substantial number of uninfected women would test positive on the first sample
- **The treatment:** no proven effective intervention for prevention of HCV transmission from mother to infant exists; antiviral therapy with ribavirin is contraindicated in pregnancy and interferon treatment is not recommended in children under three years of age

A total of 241 references were deemed to be relevant and these have been considered in this knowledge update.

The purpose of this report is to advise the UK National Screening Committee on whether any evidence has been produced which might justify changing the current policy (i.e. not to offer screening to all pregnant women) and / or whether a full review against the criteria for a screening programme is required at this point.

2. Summary of and rationale for previous review's conclusion

The last NSC review of screening for HCV in pregnancy was carried out by Lucy Pembrey in 2001 (updated in a published review paper in 2003) (1), concluded that a case could not be made for an antenatal HCV screening programme on the basis of the evidence available at that time. The current policy is that HCV screening should not be offered in pregnancy.

The rationale for the previous review's conclusion and subsequent policy is summarised below, under the NSC criteria for the introduction of a screening programme:

The condition should be an important public health problem

Hepatitis C virus (HCV) infection is a major global public health problem. Although usually remaining asymptomatic for many years, it is estimated that 85% of those infected in adulthood will develop chronic infection, approximately 20% of these will develop liver cirrhosis, and 1 to 5% of all infected adults will progress to hepatocellular carcinoma (2). Prevalence of HCV in the pregnant population was estimated to be between 0.19-0.22% in 1997-1998 (3), with around half of these infection in UK-born women; 2% of HCV seropositive women were also HIV-infected. It was estimated that there are around 70 new vertically acquired HCV infections each year in the UK.

The natural history of the condition should be understood

Vertical transmission rates are usually between 3-5%, although higher for women with very high HCV viral loads and also HIV/HCV coinfected women. Our incomplete understanding of the natural history of HCV disease in children acquiring the infection vertically was highlighted. Although there was good evidence that vertically-acquired HCV infection is relatively benign in the short to medium term (ie up to 5 years), longer-term disease progression and risk of developing the severe symptoms of HCV disease were reported to be less well understood. The impact of vertical infection with respect to the developing immune system and the potential for development of autoimmune disorders in later life was identified as a hypothetical risk.

Early detection and treatment should have benefit over later detection and treatment. Effective treatments or interventions should be available.

The pre-eminent risk for HCV transmission is HCV RNA viral load. Antiviral treatment for HCV is contraindicated in pregnancy so cannot be used to reduce risk of vertical transmission. Although some studies have indicated an association between elective caesarean section (CS) and reduced vertical transmission, it was concluded that there is insufficient evidence to support elective CS as an effective intervention for prevention of HCV vertical transmission (although this is not the case for HIV/HCV coinfected women who should be recommended to deliver by elective CS). No other established risk factor for vertical transmission was modifiable and thus the conclusion reached that no intervention can be offered to HCV infected women to reduce vertical transmission risk

There should be a valid and reliable screening test, which is safe and acceptable.

A screening test with satisfactory sensitivity and specificity was available, but the positive predictive value of the test was found to be low, due to the low HCV prevalence in pregnant women. Thus a substantial number of HCV-uninfected women would test positive on the first sample, which could result in unnecessary anxiety.

The objectives of screening should justify the costs.

The cost of screening 700,000 women each year was estimated to be about £5,700,000 and £5,900,000 when considering only the cost of ELISA tests and not personnel or other associated costs.

2. Summary of literature published since previous review.

Important public health problem

<u>Prevalence</u>

In the most recent HPA report on HCV infection it was estimated that around 185,000 individuals in the UK are chronically infected with hepatitis C. The HPA have monitored HCV infection among blood donors, a population at low risk of blood-borne viruses, as any increase in numbers of

infections might indicate an increase within the general population. Among new blood donors, 61 tested positive for HCV in 2008, approximately 0.03% overall; stratified by the two ethnic groups represented, approximate rates were 0.03% for white new donors and 0.19% from South Asian new donors. Information on risk factors was available for around three-quarters of these cases, with the two main risk factors being injecting drug use (reported in 25%) and piercing (also reported in 25%) (4). The number of HCV infections detected in new blood donors has remained relatively stable since 2004.

Prevalence in pregnancy

A new publication, based on data from 2000, presented information on the prevalence of HCV among childbearing women in Scotland from an unlinked anonymous survey: prevalence was 0.29-0.40% overall and was highest in Greater Glasgow (up to 0.96%), 25-29 year olds (up to 0.57%) and in areas of high deprivation (up to 1.07%) (5). The authors estimated that 24% of the HCV-infected women identified had been diagnosed before pregnancy; of women undiagnosed prior to pregnancy, 72% were not identified during pregnancy in the context of a de facto selective screening policy with HCV testing only offered to women with a injecting drug use history.

In the HPA 2009 report on HCV infection, some brief data on prevalence of HCV in antenatal clinics in London and Yorkshire in 2005 were provided (0.31% and 0.32% respectively), but the details of these studies have not been published. These rates are somewhat higher than the estimated prevalence in the UK in the late 1990s at 0.19-0.22% (3), but is within the range reported from Scotland in 2000 (5). The changing socio-demographic characteristics of pregnant women are one potential reason why prevalence may have changed since the last estimates were carried out in the late 1990s/2000.

With respect to HCV coinfection among the HIV-infected pregnant population, there was little evidence of overlap between the HCV and the HIV infected antenatal populations in the last UA study, with only 2% of HCV-positive women coinfected with HIV. New, but as yet unpublished, data from the UK and Ireland National Study of HIV in Pregnancy and Childhood has shown that 1.9% of pregnant HIV-infected women delivering between 2008 and 2010 had HIV/HCV coinfection overall, rising to 68% among those women with a history of injecting drug use.

Mother-to-child transmission

The range of published studies to date suggests that vertical transmission takes place in 3-8% of cases. The largest of the new analyses published since the last knowledge update comes from the European Paediatric HCV Network (EPHN) (1758 mother-child pairs), which reported a MTCT rate of 6.2% (95%CI 5.0, 7.5%) in HCV-infected women delivering between 1998 and 2004 of whom 15% were coinfected with HIV (6). The authors concluded that “there are currently no interventions to prevent MTCT”, having found no protective effect of formula feeding or elective caesarean section (CS) on transmission risk. The study was powered to detect a 60% reduction in risk associated with elective CS from 6% to 2.5% with 80% power and 5% significance. A Cochrane review of the use of elective CS for preventing HCV transmission was published in 2006, despite there being no RCTs upon which to base recommendations; the review recommended that a systematic review of evidence from observational studies should be carried out (but none has been performed to date) (7).

Until recently, studies (including the EPHN) have consistently shown an increased MTCT risk associated with HIV coinfection (8). This was no longer the case in this updated analysis from the

EPHN and the authors hypothesized that this was due to widespread use of highly active antiretroviral therapy (HAART) for HIV treatment resulting in improvements in immune function of coinfected women, with reductions in HCV viral load. However, markers of immune function were not available to test this hypothesis. Of note, among HIV/HCV coinfected women, HAART was associated with a substantial (74%) decreased risk of HCV vertical transmission, but this was only marginally statistically significant (6).

Although there is good evidence that HCV viral load is a key risk factor for MTCT, there remains an incomplete understanding of the relationship between HCV viral load and vertical transmission. There are reported cases of vertical transmissions where the mother was non-viremic, but the possibility that this was due to intermittent viremia during pregnancy or that women were misclassified due to use of insensitive viral detection tests cannot be ruled out. In the EPHN, although the crude transmission rate was nearly twice as high among the 71% of women who were viremic compared with those non-viremic (6.2% versus 3.3%), this difference did not achieve statistical significance, possibly due to small sample size and the small number of transmissions. Earlier studies documented an increase in HCV RNA load during the second and third trimesters in women with chronic HCV (9;10), and this has been confirmed in a small study from the USA (11). There is currently no evidence to suggest that preventive interventions such as elective CS might be protective among the sub-group of women with viremia. Furthermore, the studies above underscore the difficulties that would be involved in identifying such a sub-group.

Another paper from the EPHN (12) provided some new insights into the timing of vertical transmission of HCV in a sub-group of HCV-infected children with HCV RNA PCR test results available in the first 3 days of life. Results suggested that at least 31% and up to 46% of infected children acquired the infection in utero, with the remainder becoming infected intrapartum; postpartum acquisition could not be excluded but was thought to be rare. These results are consistent with the lack of evidence to support elective CS as a preventive intervention.

Natural history of vertically-acquired HCV

Although several new papers have been published on disease progression in children with HCV infection since the last review, many are from the same two groups, the Italian Observatory for HCV Infection and Hepatitis C in Children and a collaboration between clinicians in Madrid, Brussels and Italy (13-17) and involve overlapping cohorts and/or updated longitudinal analyses on the same population of children. Vertically-infected children comprise around a half of the study populations.

Key recent findings from these studies and from others (18) are summarised below:

- Reported rates of spontaneous viral clearance, whereby untreated infected children become HIV RNA negative (e.g. disappearance of HCV RNA in at least 2 consecutive serum samples taken 6 months apart) vary considerably, reflecting different definitions, methodologies and populations. In European studies, it is estimated that viral clearance may occur in around 7% to 27% of children, normally accompanied by a normalisation of ALT levels; such “clearance” appears to be more common in children with genotype 3 and in younger children. An Egyptian study reported considerably higher levels of clearance (54%) in an exclusively vertically-infected cohort (19), whilst 25% of vertically-infected children cleared the virus by 7 years of age in a Canadian study (20). In a recent single-centre study from the UK, spontaneous viral clearance was significantly lower among vertically-infected children than those infected with blood product (9% versus 27%) (18).

- Most infected children remain HCV RNA positive with persistent or intermittently abnormal ALT levels. HCV-related morbidity in these children appears to be infrequent, but a small proportion may progress to severe hepatitis or cirrhosis. For example, ~2% progressed to severe morbidity in the European studies (13;15), whilst in a small study carried out in paediatric hepatology clinics in the US, 6% of children (n=62) had evidence of cirrhosis (21). Of note, in the Italian Observatory study, the group with cirrhosis was predominantly vertically-infected (with genotype 1), with a relatively rapid progression with ages at diagnosis of cirrhosis ranging from 5 to 15 years (15). The suggestion that vertically-infected children may be at increased risk of progression to serious liver disease requires additional research.

- Longer follow-up periods of mainly parenterally infected children have indicated an increased severity of fibrosis among adolescents and those followed into young adulthood (i.e. with increasing age/duration of infection). There are insufficient data currently available to quantify the proportion of children at risk of severe morbidity during childhood or adolescence, particularly among those with vertically acquired infection due to the relatively short follow-up times in cohorts of such children.

- A further issue to consider with respect to the future health consequences of vertically acquired HCV infection is comorbidity, in particular obesity. A recent study in the USA reported that children with chronic HCV who were overweight had a greater risk of steatosis, with a trend towards more fibrosis in this group (22).

Treatment for chronic HCV infection

Treatment for HCV (interferon (IFN) and ribavirin) is contraindicated in pregnancy because of the potential for teratogenicity. This section will focus on advances made with respect to paediatric treatment and on whether there is new information on effectiveness and timing of such treatment.

<u>Paediatric treatment</u>

To date, no specific antiviral drugs for HCV have been approved for children aged less than 3 years. In the past, the only treatment available for children aged 3 years or more was IFN monotherapy, which had limited effectiveness, coupled with a poor toxicity profile. This, together with the relatively mild liver disease associated with HCV infection in childhood in general, meant that a relatively small proportion of children with chronic HCV to date have received treatment, mainly those with high ALT levels and with histological features of chronic liver inflammation. For example, in a large Italian cohort of children with chronic HCV in which enrolment started in 1990, only a quarter of children had been treated by 2007. In this cohort, 25% of those receiving IFN monotherapy achieved a sustained virological response (SVR) (lack of detectable viremia 24 weeks after cessation of therapy) (17).

However, there has been recent progress in HCV treatment in children, with the use of combination therapy of IFN or pegylated-IFN (peg-IFN) and ribavirin. Observational studies of IFN and ribavirin use in children have demonstrated SVR in around 50% (23;24). Use of peg-IFN rather than IFN has the advantage of less frequent (weekly) dosing. In a study investigating effectiveness of peg-IFN and ribavirin in children, a 59% SVR was achieved; although the treatment was well tolerated, this was not a substantial improvement compared with reported SVR with IFN and

ribavirin. Of note, all children with genotypes 2 and 3 had a SVR, but only 35% of children vertically infected with genotype 1 (25).

Two paediatric treatment studies have been published since the last evidence review, investigating the efficacy of peg-IFN with and without ribavirin in children with chronic HCV, one open-label study of 30 children (70% vertically infected) (26) and one randomised controlled trial with around 50 children in each arm (around 75% vertically infected), the PEDS-C trial (27). These studies demonstrated the superiority of combination therapy of peg-IFN with ribavirin compared with peg-IFN only. For example, in the PEDS-C trial, SVR was obtained in 53% of children randomized to combination therapy versus 21% of those in the peg-IFN and placebo arm; SVR was achieved by 53%, 93% and 80% of children infected with genotypes 1, 2-3 and 4 (27). As a result of these findings, the combination of peg-IFN and ribavirin was approved for use in children by the European Medicines Agency (EMA) in December 2009 and has become the standard of care. Of note, it is recognised that treatment is associated with side effects including flu-like symptoms, neutropenia and other haematological abnormalities. A post hoc multivariable analysis in the PEDS-C trial provided some new information on predictors of treatment success in children, reporting that female sex, non-vertical mode of acquisition, not being genotype 1, moderate to marked inflammation of the liver and lower baseline HCV RNA levels were all associated with increased probability of SVR, in addition to receipt of combination therapy versus peg-IFN alone (27); in particular, the odds of SVR was 7 times greater for parenterally infected children versus those with vertical acquisition.

Results of use of combination therapy in "real-life" settings rather than in clinical trials are just starting to be described. Sokal et al recently reported in a study of 65 children that nearly 60% of those with hard-to-treat HCV genotypes including 1 and 4, and more than 90% of those with easier-to-treat genotypes 2 or 3, achieved SVR (28). In a recent British study, 52% of children treated with IFN and ribavirin and 73% of those treated with peg-IFN and ribavirin achieved a SVR, and children with genotypes 2 or 3 were nearly nine times more likely to achieve an SVR than those with genotypes 1 or 4 (18). It has been estimated that combination therapy may improve prognosis in 50-60% of children with genotype 1, 90-100% of those with genotype 2/3 and 50% of those with genotype 4 (17). Genotyping is likely to be a useful tool to predict which children may respond most favourably to treatment.

There has long been a debate regarding indications for treatment of children with chronic HCV, with some arguing against routine treatment due to the generally mild liver disease seen in children, whilst others have pointed to the greater success rates and tolerability associated with treatment in children versus adults as a reason to treat. Given the recent treatment advances, it is likely that treatment may now be considered for larger numbers of infected children than before, and not only for those with evidence of fibrosis but also potentially for those with normal ALT levels and genotypes associated with high likelihood of SVR. Thus we may see a shift in the near future towards more widespread treatment earlier in childhood, rather than the "watchful waiting" approach that has dominated up until now.

<u>New drugs in the pipeline</u>

The protease inhibitors (PIs) currently under investigation in adult clinical trials, used as an adjunct to standard combination therapy, are likely to further influence paediatric treatment in the near future. Results from these adult clinical trials have been so impressive that Telaprevir and Boceprevir (PIs used for treatment of genotype 1) were accepted for accelerated assessment by the EMA in December 2010, reflecting recognition of a new medicine of major public health

interest, and approved for adult use in mid-2011. Clinical trial results have yet to be fully published, but results available to date demonstrate that compared with currently available treatment, Telaprevir-based combination therapy nearly doubled SVR and cut treatment time in half for most previously untreated patients; it also increased SVR three to five fold compared with standard combination therapy amongst individuals with a previous treatment failure. The question of paediatric use of these new PIs will have to be addressed, as part of the regulatory and marketing authorization procedure with the EMA in Europe.

Screening test

The positive predictive value of the antenatal screening test cannot be reassessed due to the absence of data on HCV seroprevalence in the pregnant population. Of note, rapid HCV antibody tests are now available, which can be used with oral fluid, whole blood, serum and plasma samples.

Summary

Pregnancy

- The current lack of interventions to prevent vertical transmission of HCV has been confirmed by recent studies. As such there remains no advantage in identifying maternal HCV infection during pregnancy with respect to preventing vertical transmission as there are no modifiable risk factors. The exception to this appears to be in HIV/HCV coinfected women and HCV testing is recommended for woment with HIV positive screening test results (BHIVA, Guidelines for the management of HIV infection in pregnant women (2008))
- There are no advantages to diagnosis in pregnancy with respect to management of maternal HCV disease
    - treatment is contraindicated in pregnancy
    - assessment of maternal disease is complicated by temporary, pregnancy-related changes in HCV RNA and ALT
- There may be psychological disadvantages to diagnosis in pregnancy, given the inability to intervene to reduce the probability of transmission
- The lack of data on HCV prevalence in the contemporary pregnant population in the UK is a key evidence gap

Future development

- The evidence around treatment in childhood is the main development since the previous review. This suggests that children should not be treated with IFN alone. While treatment in pregnancy remains contraindicated this may shift the debate about screening for HCV infection. This may move from a focus on screening in pregnancy to prevent mother to child transmission to screening the mother postnatally to improve the assessment / management pathway for the infant and management of the mother.
- Although a small minority of children with chronic HCV infection experience an aggressive clinical course, those infected vertically may be at increased risk. It is plausible that infection at birth (i.e. during early immune maturation) may result in differences in natural history and disease progression in vertically infected children compared with parenterally infected children acquiring HCV later in childhood
- Emerging evidence suggests that more effective treatment is now available for children with HCV (combination therapy), although such treatment is only effective in half of treated children, and appears to be substantially more effective in parenterally infected

children than in those vertically infected. It is likely that PIs will become available for paediatric use in the future for use with combination therapy, but it remains unknown whether the improved efficacy seen for adults will also apply to children.
- There is the suggestion that combination therapy in childhood may be more effective and better tolerated than that in adulthood. Whether this will apply to the use of combination therapy with PIs is unknown as this new treatment approach has not yet been evaluated in the paediatric population

Recommendations

It is recommended that:

- the current policy not to screen all pregnant women for HCV should be retained,
- the lack of knowledge regarding HCV seroprevalence in the contemporary pregnant population in the UK is addressed as a matter of urgency,
- the evidence relating to paediatric treatment and the issues relating to a postnatal screening strategy for HCV should be kept under review.

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