The role of antiviral agents in the management of viral hepatitis

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Antiviral drugs have an established role in the management of selected patients with chronic viral hepatitis. Of the hepatitis viruses (A to E), hepatitis B virus (HBV), hepatitis C virus (HCV) and hepatitis D virus (HDV) (also called delta virus) cause chronic hepatitis with the potential for development of cirrhosis and its complications, including primary hepatocellular carcinoma (HCC). HDV is seen only in the context of HBV infection and is quite rare in most countries, so the majority of physicians will see few, if any, cases of chronic HDV infection. This review will focus on the management of HBV and HCV infection and the role for antiviral therapy in the treatment and prevention of liver disease.

Acute HBV infection

Management

Most episodes of symptomatic acute HBV infection will resolve without the need for specific treatment and a role for antiviral agents is uncertain. It seems unlikely that antiviral treatment of acute HBV infection will be evaluated in randomised clinical trials so its impact on the natural history of the disease can only be guessed.

However, there is a sound rationale for the use of antiviral drugs for selected patients. In small series, high serum HBV titres were observed at the time of presentation with acute HBV infection, almost certainly reflecting high levels of viral replication. Serum HBV has the potential to infect non-infected hepatocytes, so the cycle of virus production by infected cells followed by infection of non-infected cells might be interrupted by drugs that impair virus production. Nucleoside or nucleotide analogues are most likely to fulfil this role.

Antiviral drugs may have a role for the early treatment of some patients,[1] including:

- those with severe acute hepatitis (severity reflected by prolongation of the international normalised ratio
- those with a more prolonged clinical course (eg high serum transaminases sustained for at least a week following clinical presentation)
- selected patients (eg dialysis patients and those receiving immunosuppressive drugs) who may have increased risk of development of chronicity following acute HBV infection.

Chronic HBV infection

Management

Chronic HBV infection is perceived as uncommon in the UK, but as many as 0.4% of the population may be infected. The prevalence is increasing, principally as a consequence of migration of HBV carriers to the UK from countries with high prevalence.[2] Most chronic HBV patients acquire infection at a young age, often as newborns. It may be associated with serious and important extrahepatic manifestations, such as vasculitis and nephritis, but most associated morbidity and mortality is a consequence of progression to cirrhosis and HCC.

Patient selection. Appropriate patient selection for antiviral therapy requires an understanding of the factors that influence the natural history of infection. Most patients with chronic HBV infection do not develop clinically significant liver disease. The term 'healthy carrier' was previously used to refer to these patients, implying that the long-term prognosis can be predicted and is favourable. The 'healthy carrier' is defined by the absence of significant liver damage in the context of low levels of viral replication (hepatitis B e antigen (HBeAg)-negative and serum HBV titre $<10^4$ IU/ml). However, serum titres may subsequently rise to be associated with the development of hepatic inflammation and fibrosis. Thus, a patient may not require treatment at the time of initial assessment but may need it as the liver disease evolves. Lifelong surveillance is required for most patients and the term

Key Points

Antivirals have a proven role for treatment of chronic hepatitis B and both acute and chronic hepatitis C infection

Antivirals may have a role for selected cases of acute hepatitis B infection

Antiviral therapy can prevent the development of cirrhosis and may reduce the risk for development of liver cancer in both hepatitis B and C infection

Antiviral treatment of chronic hepatitis B comprises either alpha-interferon (IFN) or nucleos(t)ide analogues

Treatment of hepatitis B aims to maintain low levels of viral replication; cure (viral eradication) is rarely achieved

Antiviral treatment of chronic hepatitis comprises the combination of alpha-interferon and ribavirin

Treatment of hepatitis C aims to eradicate infection

KEY WORDS: adefovir, hepatitis B, hepatitis C, interferon, lamivudine, ribavirin

'healthy carrier' should probably be avoided.

Antiviral treatment can alter the natural history of chronic HBV infection. For instance, effective suppression of HBV replication can:

- delay or prevent the development of liver fibrosis
- reduce the risk for progression to cirrhosis
- enable recovery from hepatic decompensation, and
- reduce the risk for development of HCC.[3,4]

Serum HBV titres. There is a clear association of serum HBV titre with risk for development of liver damage during chronic infection. Persistently low serum HBV titre ($<10^4$ IU/ml) is unlikely to be associated with progressive liver damage. High serum HBV titre appears to be prerequisite for liver damage, though some patients (particularly young HBeAg-positive patients) have high titres with little hepatic inflammation (often called the 'immunotolerant' phase of HBV infection).

Thus, high serum titre is an essential, but insufficient, indication for antiviral therapy. The likely candidate for such treatment has significant inflammatory liver disease (demonstrated biochemically and histologically) in the context of high serum HBV titres. Cohorts included in clinical trials and patients who eventually require liver transplantation show that significant liver disease is much more likely to develop in men than in women with chronic HBV infection. Therefore, the typical patient who requires antiviral treatment will be an adult man.

High serum titres may be associated with HBeAg-positive or HBeAg-negative infection. Measurement of serum HBV DNA is essential in the assessment of all patients with chronic HBV infection. HBeAg-negative hepatitis is quite common. The patient with HBeAg-negative hepatitis tends to be older than the patient with HBeAg-positive hepatitis and more likely to have advanced liver fibrosis and cirrhosis at the time of diagnosis. However, both forms of hepatitis

can be observed in patients of any age and in the same patient at different times. Patients with HBeAg-negative hepatitis have inevitably experienced a period of HBeAg-positive hepatitis at a younger age.

Antivirals have been assessed for the treatment of both HBeAg-positive and -negative infection. With respect to the effects of antiviral therapy, it is useful to consider the conditions separately.

Treatment of HBeAg-positive hepatitis

In the natural history of chronic HBeAg-positive infection, it is recognised that the disappearance of HBeAg from serum, usually accompanied by the appearance of antibodies to HBeAg (anti-HBe), is associated with a significant decline of serum HBV titre. This is accompanied by normalisation of serum transaminases and reduction of hepatic inflammation, referred to as HBeAg seroconversion. For some patients, low serum titres and normal transaminases may then be sustained for life. Assuming that seroconversion is achieved before the development of cirrhosis, these patients may not develop clinically significant liver disease. As previously indicated, however, lifelong surveillance is essential to identify the resurgence of viral replication in the context of HBeAg-negativity.

Summary of published studies. Reflecting the importance of HBeAg seroconversion in the natural history of chronic infection, most clinical trials have evaluated the impact of antivirals on the predicted spontaneous rate of HBeAg seroconversion. For instance, in placebo-controlled trials of antiviral therapy as many as 10% of placebo-treated patients may undergo 'spontaneous' HBeAg seroconversion. In most controlled trials, antivirals have raised it by a factor of 2–3 during a 6–12 month treatment period. Most published clinical trials have evaluated alpha-interferon (IFN) and nucleoside (or nucleotide) analogues.[5,6] Drugs currently licensed in the UK include IFN, lamivudine (a nucleoside analogue) and adefovir dipivoxil (a nucleotide ana-

logue). There are published data for some of the other analogues, one of which (entecavir) is licensed in North America.

It is beyond the scope of this article to review in detail the results of all published studies. The following is probably a fair summary:

- During treatment of HBeAg-positive infection, HBeAg seroconversion (including the appearance of anti-HBe) is an appropriate treatment end-point. For nucleos(t)ide analogues, treatment should be sustained for at least six months after the appearance of anti-HBe.

- Suppression of viral replication with reduction of serum HBV DNA may be observed during IFN or nucleos(t)ide treatment. Viral suppression *per se* may be beneficial, even when it occurs without HBeAg seroconversion. Prolonged viral suppression may be more feasible for nucleos(t)ide analogues than for IFN therapy.

- During short-term antiviral treatment, HBeAg seroconversion rates appear superior for IFN (threefold higher than the spontaneous rate) than for nucleos(t)ide analogues (twofold increased rate and no apparent differences between nucleos(t)ides).

- There is no apparent benefit of combination IFN/nucleos(t)ide treatment compared with IFN monotherapy.[7,8]

- Enhanced seroconversion may be seen with more prolonged treatment (better tolerated and more feasible for nucleos(t)ides than with IFN).

- Both types of treatment appear safe when supervised and monitored by experienced practitioners. Patient tolerability is superior for the nucleos(t)ide analogues.

- Despite the publication of consensus statements, there appears to be a poor consensus among physicians about the possible superiority of IFN versus nucleos(t)ide treatment in the management of

HBeAg-positive infection. Either treatment may be appropriate and the choice of drug may be determined by patient-specific or financial considerations.

- During prolonged nucleos(t)ide treatment, selection and emergence of drug-resistant HBV species may be observed.[9] The rate of emergence of drug-resistant species differs between nucleos(t)ides (much greater for lamivudine than for adefovir). When resistance is associated with a return towards baseline of serum HBV titre, the strategy for antiviral treatment needs to be reconsidered. Strategies, including the use of combinations of nucleos(t)ides, are currently under evaluation.[10,11]

- Nucleos(t)ide analogues are the treatment of choice for HBeAg-positive patients with cirrhosis, those with HBV/HIV co-infection and those receiving immunosuppression (including solid organ transplant recipients). Antiviral therapy for HBV in HBV/HIV co-infected patients should be prescribed only after consultation with the patient's HIV specialist. The appropriate choice of antivirals in this setting can suppress both HBV and HIV infections without favouring the selection of drug-resistant viral species.

Conclusions. Short-term IFN treatment or more prolonged nucleos(t)ide treatment appears to be the viable option for the antiviral treatment of HBeAg-positive infection. For the substantial proportion of patients who do not undergo HBeAg seroconversion during short-term treatment sustained inhibition of replication is a valid treatment objective. A combination of antivirals may be needed to overcome the problem of drug resistance. Though probably safe, and certainly expensive, the risk:benefit ratio of complex treatment must be assessed and justified for each patient. Such attempts may be easily justified for the treatment of patients with advanced fibrosis and cirrhosis. In this circumstance, sustained effective inhibition of replication has a palpable impact on the risk for development of liver failure (and probably reduces the risk for HCC).

Treatment of HBeAg-negative hepatitis

Antiviral treatment of HBeAg-negative hepatitis aims to suppress viral replication. Treatment should be initiated for the patient with high serum titres (either persistently or intermittently $>10^4$ IU/ml) and with evidence of significant liver damage. For HBeAg-negative infection there is not a treatment end-point equivalent to that of HBeAg seroconversion for the patient with HBeAg-positive hepatitis, but in the rare cases in which HBsAg seroconversion does occur it is a valid treatment end-point. Short-term antiviral therapy with IFN or nucleos(t)ides can achieve suppression of replication, but serum titres tend to rise when treatment is stopped.[12,13] Antiviral therapy must be sustained for most patients; both doctor and patient should accept that the duration of treatment for HBeAg-negative hepatitis is indefinite.

Summary of published studies. The following summary of antiviral treatment for HBeAg-negative hepatitis is probably fair:

- During treatment of HBeAg-negative infection, HBsAg seroconversion is an appropriate treatment end-point (although it occurs only rarely).

- During short-term antiviral treatment the HBsAg seroconversion rate appears better for IFN than for nucleos(t)ide analogues, but is very low for both.

- Suppression of viral replication with reduction of serum HBV DNA may be observed during IFN or nucleos(t)ide treatment. Prolonged viral suppression may be more feasible for nucleos(t)ide analogues than for IFN therapy.

- There is no apparent benefit of combination IFN/nucleos(t)ide treatment over IFN monotherapy.[14]

- Both types of treatment appear safe when supervised and monitored by experienced practitioners. Patient tolerability is superior for the nucleos(t)ide analogues. This is particularly relevant to the treatment of HBeAg-negative hepatitis since duration of therapy may be indefinite.

- During prolonged nucleos(t)ide treatment, selection and emergence of drug-resistant HBV species may be observed. When resistance is associated with a return towards baseline of serum HBV titre, the strategy for antiviral treatment needs to be reconsidered. Strategies, including the use of nucleos(t)ide combinations, are currently under evaluation.

Conclusions. Long-term treatment with nucleos(t)ide analogues is probably the best option for the antiviral treatment of HBeAg-negative hepatitis. Sustained inhibition of replication is the valid treatment objective. Efficacy of treatment is assessed by repeated measurement of serum HBV DNA. A combination of antivirals may be needed to overcome the problem of drug resistance. Thus, the paradigm of treatment for HBeAg-negative infection resembles that of HIV infection: both the drugs used and the approach to monitoring are similar.

General conclusions for the management of HBV infection

The following are prerequisites for the management of patients with HBV infection:

1 An understanding of the natural history of acute and chronic HBV infection.

2 An understanding of, and ready access to, the full range of HBV serological markers. In particular, patient surveillance and monitoring of antiviral therapy require repeated measurement of serum HBV DNA.

3 An understanding of nucleos(t)ide analogue resistance and ready access to drug resistance assays.

4 An ability to manage appropriately

the patient with cirrhosis, with assessment and management of portal hypertension and surveillance for liver cancer.

5   The management of special groups such as HBV/HIV co-infection and transplant recipients requires special skills and/or appropriate collaboration.

Acute HCV infection

HCV infection is most commonly acquired by high-risk behaviour, including injecting drug use. More recently, there has been an outbreak in the UK of acute HCV in men having sex with men. Acute HCV infection is usually an asymptomatic event, though some patients present with jaundice. Acute liver failure is rarely described.

Treatment

IFN is the essential component of treatment for HCV infection. However, it is more frequently associated with significant side effects than in the treatment of HBV infection. Tolerability and compliance are significant obstacles to its use, even for the treatment of carefully selected, highly motivated, psychosocially stable patients with chronic HCV infection. Recently acquired HCV infection is often an index of chaotic behaviour, implying that only a minority of patients with acute HCV infection are suitable for antiviral treatment.

A substantial proportion (possibly 50%) of patients with symptomatic acute HCV infection clear the virus without need for antiviral therapy. The decision to proceed with antiviral treatment should therefore be deferred for three months from the estimated date of acquisition. If the patient remains viraemic at that time, it is appropriate to consider antiviral treatment. This delay in treatment does not appear to compromise the very high rates of viral clearance achieved during antiviral treatment of acute HCV infection. IFN, conventional or pegylated forms, with or without ribavirin, has a high success rate for viral clearance in this setting. Pegylated IFN (PEG-IFN) for 24 weeks is

probably as good as any treatment protocol. Cure is achieved in over 80% of patients.[15]

Chronic HCV infection

As many as 0.5% of the UK population are HCV-positive. Most patients are asymptomatic and are usually diagnosed during the chronic phase of infection, frequently years or decades after acquisition, during investigation of abnormal liver function tests or when screened specifically for HCV because of previous at-risk behaviour. All HCV RNA-positive patients should be referred for specialist management.

Treatment

Selected patients will be suitable for antiviral therapy. The process of selection for treatment considers several issues:

Predicted natural history of untreated infection for specific patients. Principal determinants of natural history include age at time of infection, duration of infection, gender and alcohol consumption.[16] HCV infection has a more aggressive course in the context of immunosuppression, including HIV infection. Liver biopsy may be helpful in predicting the natural history of infection for a specific patient. For instance, a teetotal 50-year-old woman infected at the age of 20 who has a liver biopsy that demonstrates absence of fibrosis has an excellent prognosis, whereas a 50-year-old man infected at age 40 who has a heavy alcohol intake and advanced fibrosis on liver biopsy has a poor prognosis. Treatment might be justified for him but not for the woman.

Predicted life expectancy of specific patients (if HCV infection were not present). An example is a patient with serious cardiac disease or cancer for whom HCV infection may be irrelevant.

Comorbidity that might prevent or limit antiviral therapy. Usually, psychological comorbidity affects tolerability and compliance with treatment.

Social circumstances which might compromise compliance with treatment. For example, it may be wise to defer treatment for a young woman who cares for three preschool infants or a patient who has recently commenced work for a new employer. In these situations, the impact of antiviral treatment on domestic and/or work life may be unacceptable. There is never urgency to treat chronic HCV infection; deferment of treatment pending more favourable circumstances is frequently appropriate.

Predicted efficacy of antiviral therapy. Patient compliance and HCV genotype are the principal determinants of treatment efficacy. HCV genotype also determines the duration of therapy. In the UK, genotypes 1 (40–60% of cases), 2 (ca 10%) and 3 (40–60%) are most frequently observed. Treatment efficacy is greatest for type 2 (>80% success), followed by type 3 (up to 80%) and type 1 (35–45%). At present, recommended duration of treatment is 24 weeks for genotypes 2 and 3, and 48 weeks for type 1 infection. Thus, the ratio of likely benefit (cure) to cost (morbidity and financial) might favour treatment for genotypes 2 and 3 but not for type 1.

Side effects of antiviral therapy

For most chronic HCV patients, antiviral therapy comprises the combination of PEG-IFN and ribavirin.[17,18] Both drugs have significant side effects. The most common side effects of IFN treatment are flu-like symptoms (maximal initially, usually improving during treatment), weight loss, lethargy, psychological problems (principally depression) and bone marrow suppression (in particular, neutropenia can be dose-limiting). Haemolytic anaemia is the most important side effect for ribavirin.

Pegylated-interferon

At present, there are two commercially available preparations of PEG-IFN. Studies comparing the two products are ongoing but, based on existing published data, they appear to be equally efficacious. Treatment should be administered

by centres that possess appropriate expertise and manpower. Frequent review during treatment is essential, though protocols for supervision of treatment vary. Typically, patients are reviewed weekly during the first month then monthly for the duration of therapy.

Assessment of antiviral therapy

The aim of antiviral therapy is to eradicate infection. The likelihood of successful treatment is predicted by the rate of early decline in serum HCV titre. Very rapid decline is more likely to be associated with viral eradication. Thus, an assessment of the early virological response (EVR) is an essential element of management.[19] Serum HCV titres should be compared pretreatment and at week 12. If patients fail to achieve a 2-log reduction during the first 12 weeks of treatment, it is predicted that the complete course of antiviral therapy will not achieve cure. EVR is nearly always achieved for patients with genotypes 2 or 3 infection; it is usually assumed for those genotypes and virological measurements may not be made. In practice, assessment of EVR is made for patients with genotype 1 infection, for whom treatment should be abandoned at 12 weeks if EVR is not achieved – thus abbreviating the duration of treatment (and associated cost and morbidity) from 48 weeks to 12.

Most patients who achieve EVR should complete the recommended duration of therapy. Serum should be checked for HCV RNA at the conclusion of treatment, at which time it is usually undetectable. Subsequent relapse (reappearance of HCV) is observed for some patients, more frequently for genotype 1 than for the other genotypes. For those who are serum HCV RNA-negative at the end of treatment, the test should be repeated six months later. HCV RNA negativity six months post-therapy is referred to as a sustained virological response (SVR). The majority (nearly 100%) of patients who achieve SVR will remain serum HCV RNA-negative. More prolonged follow-up is essential, though virological relapse is not expected.

Summary

The combination of PEG-IFN and ribavirin given for 24–48 weeks can cure a large proportion of patients. Response rates are excellent for genotypes 2 and 3. Recent studies suggest that a treatment duration of only 12 weeks may be suitable for some patients with genotype 2 infection.[20] Results remain disappointing for genotype 1 infection. Fewer than half of treated patients are cured. A significant number of HCV-infected patients are unsuitable for, or intolerant of, IFN-based treatment. The development of HCV-specific drugs (such as the HCV serine protease inhibitor) offers promise both for these patients and for non-responders to combination treatment.[21]

Conclusions

Antiviral treatment of acute and chronic HBV and HCV has transformed the natural history of these infections. Effective treatment given to the patient who does not have cirrhosis can prevent both its development and liver failure, while the risk for development of liver cancer is substantially reduced. For HBV infection, a large proportion of patients will require suppressive treatment of indefinite duration. The principles of HIV treatment appear relevant. For HCV, antiviral treatment of finite duration appears to achieve viral eradication for many patients.

References

1 Kondili LA, Osman H, Mutimer DJ. The use of lamivudine for patients with acute hepatitis B (a series of cases). *J Viral Hepat* 2004;11:427–31.

2 Hahne S, Ramsay M, Balogun K, Edmunds WJ, Mortimer P. Incidence and routes of transmission of hepatitis B virus in England and Wales, 1995–2000: implications for immunisation policy. Review. *J Clin Virol* 2004;29:211–20.

3 Villeneuve JP, Condreay LD, Willems B, Pomier-Layrargues G *et al*. Lamivudine treatment for decompensated cirrhosis resulting from chronic hepatitis B. *Hepatology* 2000;31:207–10.

4 Liaw YF, Sung JJ, Chow WC, Farrell G *et al*. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004;351:1521–31.

5 Lai CL, Chien RN, Leung NW, Chang TT *et al*. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. *N Engl J Med* 1998;339:61–8.

6 Marcellin P, Chang TT, Lim SG, Tong MJ *et al*. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003;348:808–16.

7 Janssen HL, van Zonneveld M, Senturk H, Zeuzem S *et al*. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. *Lancet* 2005;365:123–9.

8 Leung NW, Lai CL, Chang TT, Guan R *et al*. Extended lamivudine treatment in patients with chronic hepatitis B enhances hepatitis B e antigen seroconversion rates: results after 3 years of therapy. *Hepatology* 2001;33:1527–32.

9 Ling R, Mutimer D, Ahmed M, Boxall EH *et al*. Selection of mutations in the hepatitis B virus polymerase during therapy of transplant recipients with lamivudine. *Hepatology* 1996;24:711–3.

10 Mutimer D, Pillay D, Cook P, Ratcliffe D *et al*. Selection of multiresistant hepatitis B virus during sequential nucleoside-analogue therapy. *J Infect Dis* 2000;181:713–6.

11 Perrillo R, Hann HW, Mutimer D, Willems B *et al*. Adefovir dipivoxil added to ongoing lamivudine in chronic hepatitis B with YMDD mutant hepatitis B virus. *Gastroenterology* 2004;126:81–90.

12 Tassopoulos NC, Volpes R, Pastore G, Heathcote J *et al*. Efficacy of lamivudine in patients with hepatitis B e antigen-negative/hepatitis B virus DNA-positive (precore mutant) chronic hepatitis B. Lamivudine Precore Mutant Study Group. *Hepatology* 1999;29:889–96.

13 Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang T-T *et al*; Adefovir Dipivoxil 438 Study Group. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med* 2003;348:800–7.

14 Marcellin P, Lau GK, Bonino F, Farci P *et al*. Peginterferon alpfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2004;351:1206–17.

15 Blendis L. Delayed treatment of acute HCV? Yes, but when, who, and how? *Gastroenterology* 2005;129:390–1.

16 Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR and DOSVIRC groups. *Lancet* 1997;349:825–32.

17 Manns MP, McHutchison JG, Gordon SC, Rustgi VK *et al*. Peginteferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;358:958–65.

18 Hadziyannis SJ, Sette H Jr, Morgan TR,

Balan V *et al.* Peginterferon-alpha 2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004;**140**:346–55.

19 Davis GL, Wong JB, McHutchison JG, Manns MP *et al.* Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. *Hepatology* 2003;**38**:645–52.

20 Dalgard O, Bjoro K, Hellum KB, Myrvang B *et al.* Treatment with pegylated interferon and ribavirin in HCV infection with genotype 2 or 3 for 14 weeks: a pilot study. *Hepatology* 2004;**40**:1260–5.

21 Hinrichsen H, Benhamou Y, Wedemeyer H, Reiser M *et al.* Short-term antiviral efficacy of BILN 2061, a hepatitis C serine protease inhibitor, in hepatitis C genotype 1 patients. *Gastroenterology* 2004;**127**:1347–55.

Liver disease in pregnancy

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Liver dysfunction discovered during pregnancy causes great anxiety to the patient, her family and sometimes her medical attendants. Liver disease is foreign territory to most obstetricians, while the duty physician whose opinion is sought out of hours may have only hazy knowledge of obstetric liver problems. The first on the scene is usually the on-call medical team. This review is designed to provide a guide in diagnosis and management of this relatively common problem.

Liver dysfunction can appear at any point in pregnancy and the timing is often helpful in diagnosis. There are three broad categories to consider:

- liver dysfunction specific to pregnancy
- hepatobiliary problems which occur more frequently in pregnancy (eg gallstones) or run a more serious course (eg acute hepatitis E)
- coincident liver disease which may affect management or have implications after delivery (eg chronic hepatitis B and C).

Most cases are in the first category and this review concentrates on those. The relative frequency of each of these pregnancy-specific conditions depends slightly on geography and ethnicity but is similar in most parts of the UK. The conditions in order of frequency reported in a recent prospective study from South Wales are:[1]

- liver dysfunction related to pre-eclampsia
- haemolysis, elevated liver enzymes, and low platelet count (HELLP syndrome)
- acute fatty liver of pregnancy
- obstetric cholestasis (OC)
- hyperemesis gravidarum.

Recent epidemiological data from the UK,[1,2] Northern Europe[3,4] and USA[5,6] show that OC and acute fatty liver of pregnancy (AFLP) are commoner than previously believed. This apparent increase in frequency is likely to be explained by less severe cases coming to light with improved ascertainment. Many cases of liver disease in pregnancy still remain unnoticed and undiagnosed because liver function tests (LFT) are not part of routine antenatal blood testing[1] and the symptoms may not directly suggest liver dysfunction.

Key Points

Liver dysfunction is seen in at least 3% of pregnancies and is under-diagnosed

Pregnancy-specific conditions are usually responsible

Pre-eclampsia and obstetric cholestasis are common and impact on fetal mortality

HELLP syndrome and acute fatty liver of pregnancy may rarely cause liver haemorrhage, liver failure and maternal death

Acute fatty liver of pregnancy is more common though less catastrophic than generally perceived

Boundaries between pregnancy specific liver conditions are sometimes blurred

Mechanisms are poorly defined but becoming clearer; genetic defects are only detected in a minority

KEY WORDS: acute fatty liver of pregnancy, clinical management, HELLP syndrome, hyperemesis gravidarum, incidence, intrahepatic cholestasis of pregnancy, liver disease, pre-eclampsia, pregnancy, obstetric cholestasis