THE AMERICAN JOURNAL OF GASTROENTEROLOGY
Published by Elsevier Science Inc.
Vol. 94, No. 7, 1999
ISSN 0002-9270/99/$20.00
PII S0002-9270(99)00255-5
© 1999 by Am. Coll. of Gastroenterology

PRACTICE GUIDELINES

Liver Disease in the Pregnant Patient

Caroline A. Riely, M.D., F.A.C.G.
Division of Gastroenterology, University of Tennessee, Memphis, Tennessee

PREAMBLE

Guidelines for clinical practice are intended to suggest preferable approaches to particular medical problems as established by interpretation and collation of scientifically valid research, derived from extensive review of published literature. When data are not available that will withstand objective scrutiny, a recommendation may be made based on a consensus of experts. Guidelines are intended to apply to the clinical situation for all physicians without regard to specialty. Guidelines are intended to be flexible, not necessarily indicating the only acceptable approach, and should be distinguished from standards of care that are inflexible and rarely violated. Given the wide range of choices in any health care problem, the physician should select the course best suited to the individual patient and the clinical situation presented. These guidelines are developed under the auspices of the American College of Gastroenterology and its practice parameters committee. These guidelines are also approved by the governing boards of the American Gastroenterological Association, the American Society for Gastrointestinal Endoscopy, and the American Association for the Study of Liver Diseases. Expert opinion is solicited from the outset for the document. Guidelines are reviewed in depth by the committee, with participation from experienced clinicians and others in related fields. The final recommendations are based on the data available at the time of the production of the document and may be updated with pertinent scientific developments at a later time.

INTRODUCTION

The cause of liver disease in pregnancy can be difficult to diagnose. Making the correct diagnosis is of paramount importance, as failure to do so can result in morbidity or mortality for not only the mother, but also for her fetus. Many practitioners are unfamiliar with the normal physiology of pregnancy. In addition, the practitioner in this setting is faced with disorders unique to pregnancy and thereby unfamiliar, and with disorders that commonly occur outside of pregnancy but that can be altered in their course by the pregnancy.

Pregnancy causes very few alterations in the results of standard liver tests. The aminotransferases (AST and ALT), γ-glutamyl transpeptidase (GGTP), total bilirubin, and serum bile acid level remain within the normal range. The alkaline phosphatase rises modestly in the third trimester. The albumin level is lower than in nonpregnant women, and the cholesterol level higher (1). Thus, elevations in aminotransferases or GGTP signify pathology, and should prompt a search for disease.

RECOMMENDATIONS

Use the gestational age of the pregnancy as the best guide to the differential diagnosis of liver disease in the pregnant woman.

Hyperemesis gravidarum has its onset in the first trimester. Cholestasis of pregnancy usually begins in the second trimester. The disorders associated with preeclampsia occur in the second half of pregnancy, usually in the third trimester toward term. Acute viral hepatitis in pregnancy can occur in any trimester of pregnancy, but can be more severe in the third trimester. In patients with portal hypertension, variceal bleeding usually occurs in the second trimester as the intravascular volume expands, or occurs at delivery.

Disorders Unique to Pregnancy

Hyperemesis gravidarum should be considered in the differential diagnosis of abnormal liver tests presenting in the first trimester.

Nausea is so common in early pregnancy that "morning sickness" is taken as a typical early symptom of pregnancy. In extreme cases, this leads to intractable nausea and vomiting, with dehydration and ketosis. As a rule, hyperemesis gravidarum resolves by wk 20 of gestation, but in some patients it may persist for the entire gestation. It may be accompanied by transient hyperthyroidism (2). The pathogenesis is unknown. In the modern era, the outcome is good, with no ill effects for the mother or fetus and with no increase in prematurity or birth defects (3).

Involvement of the liver is common but not invariable. The aminotransferases are abnormal in 50% of patients, usually $<$1000 U. Jaundice may occur rarely in severe cases. The liver biopsy shows minor, nonspecific changes (4). The differential diagnosis should include liver diseases associated with nausea, such as viral hepatitis, and gastrointestinal diseases such as gastric outlet obstruction from peptic ulcer disease. Viral serologies and upper endoscopy may be useful in ruling out these other disorders.

Management is empiric, aimed at alleviating the vomiting, and includes gut rest and *i.v.* fluids. No comparative

trials exist, but amtiemetics such as promethazine, odansetron, or droperidol have been reported to be useful (5, 6). Rare patients will require enteral or parenteral feeding (7). Corticosteroids have been reported to be effective (8).

Cholestasis of pregnancy is common, and should be considered in the differential diagnosis of abnormal liver tests presenting initially in the second trimester. Affected pregnancies are at increased risk for prematurity and stillbirth, and early delivery should be considered when possible.

The prevalence of cholestasis of pregnancy varies from 0.7% in the United States (9) to 6.5% in Chile (10). Itching is the cardinal symptom. The clinical spectrum is broad, ranging from modest pruritus to intractable itching associated with jaundice (11). The symptoms usually begin in the second trimester, but may start either earlier or later. The pruritus may vary in intensity during pregnancy, and it resolves within days after delivery. The pathogenesis is unclear, but it is known that affected patients are sensitive to the cholestatic effects of estrogen (12). Progesterone may be involved in the pathogenesis (13). Ethnicity and inheritance play a role (14, 15).

Laboratory tests may suggest hepatitis rather than cholestasis, as the GGTP is normal and the aminotransferases may be quite elevated ($\leq$1000 U) (16). The most useful laboratory test is the serum bile acid level, which may be measured as cholylglycine (16). Liver biopsy shows only bland cholestasis, and generally is not warranted.

Effective treatment is limited. Initial therapy is aimed at symptomatic improvement of the puritus with sedatives and antipuritics. Ursodeoxycholic acid in a dose of 13–15 mg/kg/day, divided twice a day, has shown in small controlled trials to be partially effective (13, 17). No adverse effects on the fetus have been reported, but this drug has not yet been proven to be safe in pregnancy. Cholestyramine has been used, but aggravates the fat malabsorption associated with this condition. Care should be taken in patients treated with cholestyramine to give supplementary vitamin K, which may be further depleted by the resin. S-adenosyl-methionine has been advocated as treatment, but with inconstant results (10, 18). No data exist in the literature to support the benefit of using rifampin or grapefruit juice. The only completely effective therapy is delivery.

Several studies demonstrate an increase in prematurity and sudden intrauterine death in affected pregnancies (19, 20). Unfortunately, in one study, prospective monitoring of the fetus was not effective in preventing these adverse events. Consideration should be given to early delivery, at 38 wk in most cases, and at 36 wk in severe cases if fetal lung maturity has been reached (21, 22). The only long term sequela for the mother is a modest increase in risk for gallstones (23).

HELLP (hemolysis, elevated liver tests, low platelets) syndrome and acute fatty liver of pregnancy should be considered in the differential diagnosis of abnormal liver tests in the second half of pregnancy, usually in the third trimester.

In HELLP syndrome, patients have signs of pre-eclampsia as well as thrombocytopenia. Pre-eclampsia affects 3–10% of pregnancies, and HELLP syndrome occurs in 20% of patients with severe pre-eclampsia (24). The most common symptom is abdominal pain, but it occurs in only 65% of affected patients. Many patients have no specific symptoms, and the condition is diagnosed when laboratory tests are done on patients with pre-eclampsia. Renal failure or seizures (eclampsia) may complicate the pre-eclampsia. As many as 30% of patients with HELLP present, or are diagnosed, after delivery (24). As with pre-eclampsia, the pathogenesis of this condition is unknown (25).

Aminotransferase elevations are the hallmark of this syndrome, with AST elevations ranging from 70 to 6,000, with a mean of 250 in a large series (24). This is not a true hepatic failure, and the prothrombin time is normal except in the most severe cases complicated by disseminated intravascular coagulation. The thrombocytopenia may be modest to very severe. Most patients are not jaundiced, and the hemolysis is manifested as schistocytes and burr cells on peripheral smear. The liver biopsy shows the findings typical of pre-eclampsia: periportal hemorrhage and fibrin deposition. The severity of the histological changes is not uniformly reflected in the laboratory abnormalities (26), and biopsy is not usually needed for diagnosis. The differential diagnosis includes viral hepatitis or, rarely, ITP. Viral serologies are useful.

Management is obstetrical, with careful fetal monitoring and prompt delivery. Temporizing management has been advocated by some (27), but caution is advisable. HELLP syndrome is presumed to be the initial pathology that leads, in rare cases, to subcapsular hemorrhage with hepatic rupture, often resulting in death of both the mother and fetus. Such patients present with shock and hemoperitoneum, and are best managed surgically by a trauma team experienced in liver lacerations (28). HELLP syndrome may also underlie hepatic infarction, associated with fever, very high levels of aminotransferase ($>$5000), and anemia. The infarctions are best seen on CT or MRI scanning, and resolve spontaneously (29). HELLP syndrome and hepatic hematoma may recur in subsequent pregnancies (30, 31). Once delivered, the infants have no liver involvement or thrombocytopenia and have an outcome appropriate for gestational age (32). There are no long term hepatic sequelae for the mother.

Patients with acute fatty liver of pregnancy have true hepatic dysfunction, and may, or may not, have signs of pre-eclampsia and HELLP syndrome.

Acute fatty liver of pregnancy (AFLP) is rare, reported to occur in 1/13,000–16,000 deliveries (33, 34). Like the HELLP syndrome, it may present postpartum. This may be an underestimate, as the spectrum of clinical involvement is broad, ranging from asymptomatic elevations in aminotransferases to fulminant hepatic failure with jaundice,

profound coagulopathy, hepatic coma, and hypoglycemia, requiring maximum supportive care (35). Nephrogenic diabetes insipidus may complicate the course (36).

The pathogenesis remains unclear. Preeclampsia is present in 50% of cases (37). However, the hepatic histology is distinct from that of HELLP syndrome, and involves a microvesicular fatty infiltrative disorder similar to that in Reye's syndrome. Recent studies document that infants born of affected pregnancies can be deficient in one of the enzymes of mitochondrial beta oxidation of fatty acids, long chain 3-hydroxyl-acyl CoA dehydrogenase (LCHAD) (38). Affected infants are at risk for developing nonketotic hypoglycemic coma, often with death, when stressed and fasted. Some women affected with AFLP have been shown to be heterozygous deficient for LCHAD, and it appears that many cases of AFLP are due to an inherited partial deficiency in beta oxidation of fatty acids, brought out in susceptible women by a fetus that is fully deficient, or by the stress of preeclampsia (39). Not all workers have been able to demonstrate such abnormalities (40). DNA testing in now available for several known defects in LCHAD (41).

Laboratory tests in AFLP demonstrate a long prothrombin time and low fibrinogen. The aminotransferases are usually elevated but $<$1000 U. Hypoglycemia and hyperamonemia may complicate the course. The liver biopsy shows hepatic vacuolization and pallor in the central zone, confirmed on special stains or electron microscopy to be microvesicular fat. Because of the hepatocyte unrest and portal infiltrate, the biopsy may be misread as showing viral hepatitis (35). The differential diagnosis includes fulminant hepatic failure of other etiologies, especially viral, such as hepatitis E in endemic areas (42), or herpes simplex (43). HELLP syndrome may be in the differential diagnosis, if the platelet count is low because of attendant severe liver disease with disseminated intravascular coagulation. Given the clinical setting, liver biopsy usually is not indicated.

Management consists of prompt delivery with maximal support as the liver recovers. Liver transplantation has been done for AFLP (44), but should not be necessary with early diagnosis and delivery. Because of the association with LCHAD deficiency, consideration should be given to testing both the mother and child for this disorder.

Liver Disorders Coincidental With Pregnancy

Consider viral or drug-induced hepatitis, gallstone disease, or malignancy in the differential diagnosis of abnormal liver tests in any of the trimesters of pregnancy.

Pregnant women may be affected by intercurrent diseases during pregnancy, and some of these are exacerbated by the underlying pregnant state. Viral hepatitis is the most common liver disease, and acute viral hepatitis can present problems in the pregnant woman. The natural course of acute hepatitis A or B is not altered in the pregnant woman, and interruption of the pregnancy or early delivery is not indicated. But acute hepatitis B in the second or third trimester may pose a risk for transmission to the baby, and immunoprophylaxis with hepatitis B hyperimmune globulin as well as the standard vaccination program is indicated for the neonate. For unclear reasons, both herpes simplex and hepatitis E, which is endemic in the Middle East and in Asia but has not been reported in the United States except in travelers, can cause fulminant hepatic failure with a high maternal mortality when affecting the pregnant woman, particularly during the third trimester (42, 43). Hepatitis serologies are useful in the differential diagnosis of possible viral hepatitis in pregnancy. A history of potential exposure should be sought. Typically, patients with herpes simplex have marked elevations of aminotransferases (3000–6000 U) but are not jaundiced. Such patients usually have a rash and can be effectively treated with intravenous acyclovir, thus not requiring early delivery (43).

Pregnancy predisposes to gallstone disease, and the biliary sludge and gallstones that form during pregnancy may resolve after delivery with the return to nonpregnant physiology (45, 46). If possible, acute cholecystitis is best managed medically in the first and third trimesters, when the risk of premature delivery prompted by surgery is greater than in the second trimester. Choledocholithiasis can be managed with endoscopic retrograde cholangiography, which may be necessary in the management of symptomatic common bile duct stones leading to cholecystitis or pancreatitis (47).

Pregnancy is associated with a heightened procoagulant state, and patients who have an underlying procoagulant state, such as an inherited deficiency in protein C or protein S, or the presence of an anticardiolipin or antiphospholipid antibody, may be at an increased risk for thromboses during pregnancy (48, 49). This may take the form of Budd-Chiari syndrome, thrombosis of the major hepatic outflow tract, leading to painful hepatomegaly, often with liver failure, and portal hypertension with ascites. Liver transplantation may be necessary in this setting (50). Life-long anticoagulation is indicated in patients who survive.

Malignancy with metastases to the liver may occur in pregnancy, and there may be some permissive effect of pregnancy promoting tumor growth (51). The presence of a palpable liver during pregnancy, when the liver is usually forced up under the rib cage, is ominous, and should prompt investigation with laboratory tests and imaging (52).

Chronic hepatitis B or C requires no therapy in pregnancy, but poses a risk of transmission to the offspring.

Pre-existing liver disease, when severe, usually is not compatible with pregnancy, and such patients are anovulatory and infertile. However, most patients who are chronically infected with hepatitis B or hepatitis C are well, and can conceive and carry the gestation with no increased risk to themselves. There is, however, a risk to their offspring. For women with hepatitis B who are hepatitis Be antigen–positive, the risk of transmission of the virus to the baby is 90% (53). Because of this risk, all pregnant women are now screened for the presence of hepatitis Bs antigen (54, 55). If positive, the infant is passively immunized at birth with

hepatitis B hyperimmune globulin along with the hepatitis B vaccine that is now given as a standard to all newborns. The risk of transmission of hepatitis C is substantially lower (6–10%) and depends on the mother's level of viremia (56). For example, the risk of hepatitis C transmission is higher for mothers with HIV, who have high levels of hepatitis C viremia. Unfortunately, no effective immunoprophylaxis is available for lowering this risk, and gamma globulin does not prevent transmission. Breast feeding is safe for the offspring of mothers with hepatitis B, once appropriately immunized, and with hepatitis C (57).

Patients with autoimmune hepatitis or with Wilson's disease improve on therapy, regain their fertility, and can conceive. Such patients should continue their therapy during the pregnancy (58, 59). Like all patients with chronic liver disease, they are at increased risk for preeclampsia and premature delivery (60).

Many survivors of liver transplantation are young women, who return to normal fertility after the transplant. Like the patients with chronic liver disease, they are at increased risk for pregnancy complications such as hypertension or prematurity, but their infants do not have an increased risk for birth defects (61).

Reprint requests and correspondence: Caroline A. Riely, M.D., F.A.C.G., Division of Gastroenterology, University of Tennessee, Room 555-Dobbs, 951 Court Avenue, Memphis, TN 38163.
Received Feb. 9, 1999; accepted Feb. 18, 1999.

REFERENCES

1. Bacq Y, Zarka O, Brechot J-F, et al. Liver function tests in normal pregnancy: A prospective study of 103 pregnant women and 103 matched controls. Hepatology 1996;23: 1030–4.
2. Goodwin T, Montoro M, Mestman J. Transient hyperthyroidism and hyperemesis gravidarum: Clinical aspects. Am J Obstet Gynecol 1992;167:648–52.
3. Hallak M, Tsalamandris K, Dombrowski M, et al. Hyperemesis gravidarum. Effects on fetal outcome. J Reprod Med 1996; 41:871–4.
4. Abell T, Riely C. Hyperemesis gravidarum. Gastroenterol Clin North Am 1992;21:835–49.
5. Sullivan CA, Johnson CA, Roach H, et al. A pilot study of intravenous ondansetron for hyperemesis gravidarum. Am J Obstet Gynecol 1996;174:1565–8.
6. Nageotte M, Briggs G, Towers C, et al. Droperidol and diphenhydramine in the management of hyperemesis gravidarum. Am J Obstet Gynecol 1996;174:1801–5; discussion 1805–6.
7. Hsu J, Clark-Glena R, Nelson D, et al. Nasogastric enteral feeding in the management of hyperemesis gravidarum. Obstet Gynecol 1996;88:343–6.
8. Nelson-Piercy C, DeSwiet M. Corticosteroids for the treatment of hyperemesis gravidarum. Br J Obstet Gynaecol 1994; 101:1013–5.
9. Wilson J, Carrington E. Obstetrics and gynecology. St. Louis: CV Mosby, 1979.
10. Ribalta J, Reyes H, Gonzalez M, et al. S-adenosyl-L-methionine in the treatment of patients with intrahepatic cholestasis of pregnancy: A randomized, double-blind, placebo-controlled study with negative results. Hepatology 1991;13:1084–9.
11. Reyes H. The enigma of intrahepatic cholestasis of pregnancy: Lessons from Chile. Hepatology 1982;2:87–96.
12. Reyes H, Ribalta J, Gonzalez M, et al. Sulfobromophthalein clearance tests before and after ethinyl estradiol administration, in women and men with familial history of intrahepatic cholestasis of pregnancy. Gastroenterology 1981;81:226–31.
13. Meng L, Reyes H, Axelson M, et al. Progesterone metabolites and bile acids in serum of patients with intrahepatic cholestasis of pregnancy: Effect of ursodeoxycholic acid therapy. Hepatology 1997;26, No 6:1573–9.
14. Holzbach R, Sivak D, Braun W. Familial recurrent intrahepatic cholestasis of pregnancy: A genetic study providing evidence for transmission of a sex-limited, dominant trait. Gastroenterology 1983;85:175–85.
15. Reyes H, Simon F. Intrahepatic cholestasis of pregnancy: An estrogen-related disease. Sem Liver Dis 1993;13:289–301.
16. Bacq Y, Sapey T, Brechot M, et al. Intrahepatic cholestasis of pregnancy: A French prospective study. Hepatology 1997;26: 358–64.
17. Palma J, Reyes H, Ribalta J. Effects of ursodeoxycholic acid in patients with intrahepatic cholestasis of pregnancy. Hepatology 1992;15:1043–7.
18. Frezza M, Pozzato G, Chiesa L, et al. Reversal of intrahepatic cholestasis of pregnancy in women after high dose S-adenosyl-L-methionine administration. Hepatology 1984;4:274–8.
19. Reyes H, Radrigan M, Gonzalez M, et al. Steatorrhea in patients with intrahepatic cholestasis of pregnancy. Gastroenterology 1987;93:584–90.
20. Rioseco A, Ivankovic M, Manzur A, et al. Intrahepatic cholestasis of pregnancy: A retrospective case-control of perinatal outcome. Am J Obstet Gynecol 1994;170:890–5.
21. Alsulyman O, Ouzounian J, Ames-Castro M, et al. Intrahepatic cholestasis of pregnancy: Perinatal outcome associated with expectant management. Am J Obstet Gynecol 1996;175: 957–60.
22. Matos A, Bernardes J, Ayres-de-Campos D, et al. Antepartum fetal cerebral hemorrhage not predicted by current surveillance methods in cholestasis of pregnancy. Obstet Gynecol 1997; 89:803–4.
23. Hirvioja M, Kivinen S. Inheritance of intrahepatic cholestasis of pregnancy in one kindred. Clin Genet 1993;43:315–7.
24. Sibai B, Ramadan M, Usta I, et al. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). Am J Obstet Gynecol 1993;169:1000–6.
25. Broughton Pipkin F. The hypertensive disorders of pregnancy. Br Med J 1995;311:609–13.
26. Barton J, Riely C, Adamec T, et al. Hepatic histopathologic condition does not correlate with laboratory abnormalities in HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). Am J Obstet Gynecol 1992;167:1538–43.
27. Visser W, Wallenburg H. Temporising management of severe pre-eclampsia with and without the HELLP syndrome. Br J Obstet Gynaecol 1995;102:111–7.
28. Stevenson J, Graham D. Hepatic hemorrhage and the HELLP syndrome: A surgeon's perspective. Am Surgeon 1995;61: 756–60.
29. Krueger K, Hoffman B, Lee W. Hepatic infarction associated with eclampsia. Am J Gastroenterol 1990;85:588–92.
30. Sullivan C, Magaan E, Perry KJ, et al. The recurrence risk of the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP) in subsequent gestations. Am J Obstet Gynecol 1994;171:940–3.
31. Greenstein D, Henderson J, Boyer T. Liver hemorrhage: Re-

current episodes during pregnancy complicated by preeclampsia. Gastroenterology 1994;106:1668–71.
32. Harms K, Rath W, Herting E, et al. Maternal hemolysis, elevated liver enzymes, low platelet count, and neonatal outcome. Am J Perinatol 1995;12:1–6.
33. Pockros P, Peters R, Reynolds T. Idiopathic fatty liver of pregnancy: Findings in ten cases. Medicine 1984;68:1–11.
34. Reyes H, Sandoval L, Wainstein A, et al. Acute fatty liver of pregnancy: A clinical study of 12 episodes in 11 patients. Gut 1994;35:101–6.
35. Riely C, Latham P, Romero R, et al. Acute fatty liver of pregnancy: A reassessment based on observations in nine patients. Ann Intern Med 1987;106:703–6.
36. Cammu H, Velkeniers B, Charels K, et al. Idiopathic acute fatty liver of pregnancy associated with transient diabetes insipidus. Case report. Br J Obstet Gynecol 1987;94:173–8.
37. Riely C. Acute fatty liver of pregnancy. Sem Liv Dis 1987; 7:47–54.
38. Wilcken B, Leung K-C, Hammond J, et al. Pregnancy and fetal long-chain 3-hydroxyacyl coenzyme A hydrogenase deficiency. Lancet 1993;341:407–8.
39. Treem W, Shoup M, Hale D, et al. Acute fatty liver of pregnancy, hemolysis, elevated liver enzymes, and low platelets syndrome, and long chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency. Am J Gastroenterol 1996;91:2293–2300.
40. Mansouri A, Fromenty B, Durand F, et al. Assessment of the prevalence of genetic metabolic defects in acute fatty liver of pregnancy. J Hepatol 1996;25:781.
41. Sims H, Brackett J, Powell C, et al. The molecular basis of pediatric long chain 3-hydroxyacyl-CoA dehydrogenase deficiency associated with maternal acute fatty liver of pregnancy. Proc Natl Acad Sci USA 1995;92:841–5.
42. Hamid S, Jafri S, Khan H, et al. Fulminant hepatic failure in pregnant women: Acute fatty liver or acute viral hepatitis. J Hepatology 1996;25:20–7.
43. Klein N, Mabie W, Latham P, et al. Herpes simplex virus hepatitis in pregnancy. Gastroenterology 1991;100:239–44.
44. Ockner SA, Brunt EM, Cohn SM, et al. Fulminant hepatic failure caused by acute fatty liver of pregnancy treated by orthotopic liver transplantation. Hepatology 1990;11:59–64.
45. Maringhini A, Marceno MP, Lanzarone F, et al. Sludge and stones in gallbladder after pregnancy. Prevalence and risk factors. J Hepatol 1987;5:218–23.
46. Tsimoyiannis E, Antoniou N, Tsaboulas C, et al. Cholelithiasis during pregnancy and lactation. Prospective study. Eur J Surg 1994;160:627–31.
47. Jamidar P, Beck G, Hoffman B, et al. Endoscopic retrograde cholangiopancreatography in pregnancy. Am J Gastroenterol 1995;90:1263–7.
48. Segal S, Shenhav S, Segal O, et al. Budd-Chiari syndrome complicating severe preeclampsia in a parturient with primary antiphospholipid syndrome. Eur J Obstet Gynecol Reprod Biol 1996;68:227–9.
49. Ouwendijk R, Koster J, Wilson J, et al. Budd-Chiari syndrome in a young patient with anticardiolipin antibodies: Need for prolonged anticoagulant treatment. Gut 1994;35:1004–6.
50. Fickert P, Ramschak H, Kenner L, et al. Acute Budd-Chiari syndrome with fulminant hepatic failure in a pregnant woman with factor V Leiden mutation. Gastroenterology 1996;111: 1670–3.
51. Maeta M, Yamashiro H, Oka A, et al. Gastric cancer in the young, with special reference to 14 pregnancy-associated cases: analysis based on 2,325 consecutive cases of gastric cancer. J Surg Oncol 1995;58:191–5.
52. Gamberdella F. Pancreatic carcinoma in pregnancy: A case report. Am J Obstet Gynecol 1984;149:15–7.
53. Arevalo J. Hepatitis B in pregnancy. West J Med 1989;150: 668–74.
54. Program to prevent perinatal hepatitis B virus transmission in a health-maintenance organization—North California, 1990–1995. Morb Mortal Wkly Rep 1997;46:378–80.
55. Hollinger F. Comprehensive control (or elimination) of hepatitis B virus transmission in the United States. Gut 1996; 38(suppl 2):S24–30.
56. Ohto H, Terazawa S, Sasaki N, et al. Transmission of hepatitis C virus from mothers to infants. N Engl J Med 1994;330:744–50.
57. Lin H, Kao J, JY J, et al. Absence of infection in breast-fed infants born to hepatitis C virus-infected mothers. J Pediatr 1995;126:589–91.
58. Lee M, Hanchard B, Donaldson E, et al. Pregnancy in chronic active hepatitis with cirrhosis. J Trop Med Hyg 1987;90: 245–8.
59. Walshe J. The management of pregnancy in Wilson's disease treated with trientine. Q J Med 1986;58:81–7.
60. Steven MM, Buckley J, Mackay I. Pregnancy in chronic active hepatitis. Q J Med 1979;48:519–31.
61. Radomski J, Moritz M, Munoz S, et al. National transplantation pregnancy registry: Analysis of pregnancy outcomes in female liver transplant recipients. Liver Transplant Surg 1995; 1:281–4.