Pregnancy and the biliary system

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ABSTRACT: Alterations in the synthesis and secretion of bile salts and cholesterol and in gallbladder function occur during pregnancy. These changes are related to the effects of estrogen and progesterone. Biliary cholesterol saturation and the cholic acid/chenodeoxycholic acid ratio increase. Progesterone also diminishes gallbladder contractility and emptying. Gallstones occur in 2.5 to 11% of pregnant women and are associated with cholecystitis in 0.008 to 0.1% of pregnant women. Operative treatment should be deferred if possible until after delivery; failing that, surgery is best done in the second trimester. Endoscopic papillotomy may prove to be the best therapy for choledocholithiasis. *Can J Gastroenterol* 1990;4(5):209-214

Key Words: Biliary tract, Gallstones, Pathophysiology, Pregnancy, Treatment

La grossesse et le système biliaire

RESUME: La synthèse et la sécrétion des sels biliaires et du cholestérol ainsi que la fonction de la vésicule biliaire sont modifiées pendant la grossesse. Ces changements sont reliés à l'action de l'oestrogène et de la progestérone. La saturation de la bile native en cholestérol et le rapport acide cholique/acide chénodésoxycholique augmentent. La progestérone réduit également la contractilité et l'évacuation de la vésicule. Les calculs surviennent chez 2,5 à 11% des femmes enceintes et sont associés à la cholécystite chez 0,008% à 0,1% d'entre elles. Le traitement opératoire devrait si possible être retardé après l'accouchement ou devrait alors s'effectuer de préférence au cours du second trimestre. La papillotomie endoscopique est probablement la thérapie la plus appropriée à la cholédocolithiase.

reported during pregnancy include: choledochal cysts, biliary tract carcinoma and rupture of the cystic duct. In general, these lesions are not related to pregnancy per se, and their frequency is similar to that in the nonpregnant population; at best there is a weak association.

This review will examine disorders of the biliary tree in pregnancy, with emphasis on the pathogenesis and management of gallstone disease.

NORMAL PHYSIOLOGY

Prior to discussion of the pathophysiology of biliary tract disease in pregnancy, a brief review of the normal physiology is appropriate.

The chief constituents of bile are bile salts, cholesterol, phospholipids, bilirubin, electrolytes and water. Bile salts are conjugated bile acids synthesized in the liver from cholesterol. Their main function is to emulsify dietary fat and thus aid in the digestion and absorption of lipids. Excreted bile acids consist of recirculated bile acids, the major constituent, and newly synthesized bile acids (2).

The rate of synthesis of primary bile acids (cholic and chenodeoxycholic acid) from cholesterol in the liver is regulated by the activity of 7- α -hydroxylase. The activity of this enzyme is under negative feedback control, dependent on the quantity of bile salts returning to the liver via the enterohepatic circulation (3).

biliary colic, acute cholecystitis and pancreatitis. During pregnancy, cholecystectomy is second only to appendectomy as a nonobstetric cause of laparotomy (1).

Other rarer lesions of the biliary tree

DURING PREGNANCY, BILE FORMATION and gallbladder function undergo specific changes which predispose to the development of cholelithiasis. In most patients, gallstones are asymptomatic, but in some they cause

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The primary bile acids are conjugated with glycine and taurine, and then secreted into bile canaliculi. When they are present above a critical concentration, aggregation occurs, leading to micelle formation. Micelles have a hydrophobic centre and a hydrophilic exterior. This property allows water-insoluble compounds to be maintained in solution (4).

Cholesterol and lecithin are water-insoluble compounds. The incorporation of lecithin, a phospholipid, into the micelle results in increased cholesterol-carrying capacity. The solubilization of cholesterol by these 'mixed' micelles is an important factor in the prevention of gallstone formation. Solubility limits of cholesterol relative to bile salt and lecithin concentrations have been well defined (5,6). Outside these solubility limits bile is supersaturated with cholesterol. The term 'lithogenic bile' refers to its predisposition to gallstone formation.

Differences in 'coupling ratios' (ie, the amount of cholesterol carried per molecule of bile salt) exist between the two primary bile acids. The capacity of cholate to couple with cholesterol is greater than that of chenodeoxycholate. This accounts in part for the litholytic properties of chenodeoxycholate compared to the lithogenic properties of cholate (7). In addition to the solubility of cholesterol, other factors which play a role in stone formation include nucleating (8) and antinucleating factors (9). These enhance or discourage stone formation, respectively, but are of lesser importance compared to the solubility limits of cholesterol. The role of phospholipid vesicles in transporting biliary cholesterol and in the etiology of gallstones is still being explored.

Bile is stored in the gallbladder until the gallbladder contracts and empties its contents into the duodenum. About 90% of bile salts are actively absorbed in the distal ileum by diffusion (10). These bile acids then return to the liver via the portal circulation to complete the enterohepatic circulatory cycle. Bile salts reaching the colon are deconjugated by bacterial 7- α -dehydroxylase to secondary bile salts (deoxycholic and lithocholic acid) and are excreted in

the stool. Thus 90 to 95% of the bile salt load is conserved and recycled five to seven times per day (11).

Any mechanism whereby bile cholesterol concentration is increased or bile acid concentration decreased favours the formation of cholesterol cholelithiasis, the principal disease of the biliary tract in pregnancy. Pathogenetic factors specific to pregnancy will be discussed in further detail in the pathophysiology section.

EPIDEMIOLOGY OF GALLSTONE DISEASE IN PREGNANCY

There is substantial worldwide variation in the incidence of gallstones. In the United States, post mortem studies indicate that about 15% of the adult population has gallstones (12). Clearly, such studies are potentially biased by the age of the autopsy population. Eighty-five to 95% of these gallstones are primarily composed of cholesterol, whereas in southeast Asia bilirubin stones are more common (13). Recent Scandinavian studies have reported a significant decline in gallstone incidence which has been attributed to both decreased use of contraceptives and reduced contraceptive hormonal content (14-16).

The Framingham study (17) reviewed the rate of definite gallbladder disease (defined by autopsy or surgery) and found an increasing 10 year incidence rate for women as follows: age groups 30 to 39, 40 to 49 and 50 to 62 had respective incidence rates of 30, 66 and 89 per 100,000. These figures show an increase in gallstone disease with increasing age. In support of this, age has also been shown a positive correlation with rate of cholesterol secretion and a negative correlation with bile acid synthesis, both of which predispose to lithogenic bile (18).

Females are twice as likely to develop cholelithiasis as men (17). This difference becomes apparent at menarche and continues through the child-bearing years (19). It should be noted, however, that with increasing age comes increasing development of gallstones in both men and women (17,20).

Obesity is positively correlated with

cholelithiasis, possibly because of the increased rate of cholesterol secretion in association with an unchanged bile salt secretory rate (21,22).

Although the influence of pregnancy on gallstone incidence has been recognized for many years, the relationship is not quite as clearcut as was formerly thought. The Framingham study (17) showed that parity increased the risk of gallstone formation after four or more pregnancies. More recent studies have confirmed the association with pregnancy but suggest that the increased risk is confined to younger pregnant women. Scragg (23) found that as the age of first pregnancy increased, the risk of gallstone fell. Similarly, the increased incidence of gallstones in contraceptive users is confined to women less than 29 years of age. These findings imply that pregnancy and female sex hormones unmask a subpopulation of younger women who are particularly susceptible to cholelithiasis.

In summary, the major risk factors for cholesterol gallstones are female gender, pregnancy, obesity, age and racial origin.

PATHOGENESIS OF GALLSTONE FORMATION IN PREGNANCY

Changes in both bile chemistry and gallbladder motility have been offered as an explanation for the epidemiological association of pregnancy and oral contraceptives with increased gallstone formation.

Cholesterol saturation of bile and rate of secretion of cholesterol are increased by both pregnancy and female sex steroids (24,25). In addition, pregnancy and sex steroids lead to an increased ratio of cholic acid to chenodeoxycholic acid in bile. The net result is increased bile lithogenicity.

Kern (26) found that administration of oral contraceptive medications led to increased secretion of biliary cholesterol, which directly paralleled cholesterol synthesis and hepatic uptake of chylomicron remnants. In a companion publication (27), the same workers reported a direct relationship between both bile acid and cholesterol synthesis in response to contraceptive

steroids. In this setting, estrogen and progesterone caused a preferential increase in cholic acid relative to chenodeoxycholic acid, thus enhancing the lithogenic tendency of bile. It was suggested that estrogen and progesterone have different effects, estrogen acting mainly to increase hepatic uptake of cholesterol possibly by increasing receptor activity, and progesterone causing increased hepatocyte secretion of cholesterol by inhibiting the activity of the cholesterol-esterifying enzyme acyl-coenzyme A: cholesterol acyltransferase. The effect of estrogen on hepatic cholesterol uptake is supported by another study in postmenopausal women in whom estrogen administration increased biliary cholesterol without affecting intestinal absorption or hepatic synthesis (28).

The role of phospholipid vesicles or nucleating and antinucleating factors in stone formation has not been explored during pregnancy or in response to sex hormones.

A recent prospective study from Italy (29) has demonstrated the dynamic nature of gallstone formation and dissolution during pregnancy. The formation of both sludge and stones increased progressively during pregnancy with a cumulative incidence of sludge and stones immediately after delivery of 41 and 9.6%, respectively. In many of these women, sludge and stones disappeared both during and following pregnancy.

The effects of estrogen on biliary cholesterol saturation are supported by a recent study on estrogen-induced gallstone formation in males. The patients were being treated for carcinoma of the prostate with estrogen, which resulted in five of 37 patients on estrogen developing gallstones, while none of the control orchidectomy patients developed stones. Biliary lipids and phospholipids also increased and chenodeoxycholic acid decreased moderately in the estrogen-treated group (30).

Pregnancy also has a deleterious effect on gallbladder contractility which begins during the second trimester (31) and results in increases in gallbladder

volume during fasting – as well as in residual volume after contraction – which are twice those of nonpregnant females (31,32). There is also a decreased rate (31) and percentage (31,33) of emptying. The common bile duct size remains within normal limits (34).

Progesterone is believed responsible for these effects by inhibition of smooth muscle function. Experiments using pregnant guinea pigs show decreased gallbladder contractility in response to acetylcholine and cholecystokinin, but no change in the face of increased extracellular potassium. This result suggests that progesterone may specifically affect a step in the excitation-contraction coupling process common to both acetylcholine and cholecystokinin (35).

It is believed that the combination of gallbladder stasis and lithogenic bile allows formation of cholesterol crystals and eventual gallstones.

CLINICAL ASPECTS OF CHOLELITHIASIS IN PREGNANCY

The major areas to be discussed relate to differences in incidence, clinical features, diagnosis and management of symptomatic gallstones in pregnancy.

Incidence: Although there is good evidence for the *de novo* formation of gallstones and sludge during pregnancy, it is not clear from the available literature whether there is also an increase in the incidence of symptomatic gallstone disease. At any rate, biliary tract problems are relatively uncommon in pregnant women, falling well behind appendicitis as a cause of nonobstetric laparotomy. The incidence of gallstones in pregnancy has been quoted as ranging from 2.5 to 11.3% (37-39), but any consideration of these figures must take into account the tendency towards increased stone formation throughout pregnancy, as well as the dynamic nature of stone formation and dissolution. The prevalence of acute cholecystitis in pregnancy ranges from 0.008 to 0.1% (1,40).

Clinical features: The manifestations of biliary colic are similar in pregnant and nonpregnant women. Pain, which lasts up to several hours, is situated in the epigastrium or right hypo-

chondrium (41-43). There is no specific relationship to ingestion of fatty foods, and in the nonpregnant patient, biliary colic is more common during the night versus day time. Unlike peptic ulcer pain, its occurrence is unpredictable, and episodic upper abdominal pain occurring daily is unlikely to be due to biliary colic.

Acute cholecystitis may occur at any time during pregnancy. It causes more severe pain of longer duration than biliary colic and is associated with tenderness and guarding in the right hypochondrium. Varying degrees of fever, vomiting, tachycardia and hypotension occur, depending on the severity of gallbladder sepsis.

The course of acute cholecystitis may be complicated by jaundice due either to the spread of inflammatory edema to the common bile duct, or to choledocholithiasis (44). The latter problem may also give rise to pancreatitis or cholangitis (45,46). Acute cholecystitis must be distinguished from appendicitis, pancreatitis, perforated peptic ulcer, pneumonia, acute fatty liver of pregnancy and pre-eclampsia, all of which can cause similar findings.

INVESTIGATIONS

Biochemistry: Uncomplicated biliary colic causes no changes in liver function tests or white cell count. Acute cholecystitis may be accompanied by a varying degree of leukocytosis and changes in liver function caused either by adjacent hepatic inflammation, common duct edema or choledocholithiasis. Accordingly, depending on the relative contributions of these changes, either the aminotransferases or alkaline phosphatase may be increased. Acute cholecystitis may also be accompanied by an up to twofold elevations of serum amylase (44). Greater rises in amylase raise the possibility of either acute pancreatitis or choledocholithiasis.

Pregnancy is normally associated with raised levels of alkaline phosphatase of placental origin which may be a source of confusion. Measurement of gamma-glutamyl transferase can help confirm the hepatic origin of alkaline

phosphatase. Other hepatic complications of pregnancy such as acute fatty liver or pre-eclampsia will also affect liver function tests.

Ultrasound: The advent of ultrasonic scanning has provided a safe, simple, rapid and accurate method of evaluating patients with possible gallbladder disease, making the need for oral and intravenous cholangiography virtually obsolete. Ultrasound has become increasingly accurate with time, and 95 to 99% accuracy in diagnosing cholelithiasis has been reported (47). The ultrasonic diagnosis of acute cholecystitis has a sensitivity of 94%, a specificity of 85% and an overall accuracy of 88% (48). Aside from visualization of gallstones themselves, pericholecystic fluid, distension and thickening of the gallbladder wall, and ultrasound transducer-induced pain over the gallbladder are suggestive of cholecystitis (49). The demonstration of dilated bile ducts on ultrasound examination is most likely due to choledocholithiasis and should be confirmed by endoscopic retrograde cholangiopancreatography, which can be followed by endoscopic papillotomy.

Nonvisualization of the gallbladder on radioisotope scanning may confirm the presence of cholecystitis, but because of radiation risk to the fetus, albeit small, scanning should only be performed if the diagnosis remains unclear and the patient is deteriorating.

MANAGEMENT AND TREATMENT

Asymptomatic stones in the gallbladder of a nonpregnant individual should be left alone (1). Pregnant patients who develop acute cholecystitis should receive conservative management initially, consisting of nasogastric suction, intravenous fluids, analgesics and antibiotics (if sepsis is suspected) (1,42,43,50). Resolution rates of 77 (51) to 84% (52) can be expected with medical treatment.

The timing of elective cholecystectomy following an episode of acute cholecystitis in pregnancy is controversial. Some surgeons advocate cholecystectomy during the second trimester, whereas others feel that the likelihood of a second attack is sufficiently small,

and its outcome sufficiently benign to warrant postponing elective operation until after delivery. The greatest hazard of waiting relates to unsuspected choledocholithiasis, but the increasing availability of endoscopic papillotomy diminishes this risk. In areas where ready access to skilled endoscopy is limited, one may argue for a more aggressive approach to cholecystectomy during pregnancy, especially during the second trimester, if liver function tests are abnormal or bile ducts dilated.

If surgical intervention is unavoidable, then the second trimester is considered an optimal period, since the highest risk period for spontaneous abortion has passed and the uterus has not yet obscured the surgical field (1,43,52,53).

Maternal morbidity and mortality do not differ from that of the nonpregnant population (39,41). Fetal mortality is approximately 5% (39,53) but can be as high as 15% if surgery takes place in the first trimester (54,55).

In the case of patients with choledocholithiasis during pregnancy, endoscopic papillotomy will likely become the treatment of choice (56). Complications of this procedure include bleeding, pancreatitis, cholangitis and duodenal perforation. The complication rate in skilled hands is less than 5%, and appropriate shielding can diminish radiation exposure of the fetus. In view of the young age of these patients and the possibility of further gallbladder – as opposed to bile duct – complications, elective cholecystectomy should be done after delivery.

Gallstone pancreatitis has been associated with a high fetal mortality of 60% (57), but a more recent study did not support these figures and proposed that the poor fetal outcome previously reported was a direct result of laparotomy done early in pregnancy (46).

OTHER LESIONS

There are a number of reports of choledochal cysts becoming symptomatic during pregnancy (58,59). Such cysts usually present at an early age and are more common in females (4:1 ratio) and Orientals. Of the four types of cysts, type 1 is encountered

most frequently. This type is defined as spherical dilatation of the common bile duct with distal narrowing (58). Typical features include pain, jaundice and right upper quadrant mass.

It has been suggested that the compressive effect of the enlarging uterus impairs emptying of the choledochal cyst, leading to the development or worsening of symptoms related to the cyst (59). The coincidental finding of a cholangiocarcinoma complicating a choledochal cyst in pregnancy has been reported (60).

Treatment of asymptomatic cysts can be deferred until after delivery, at which time the appropriate treatment consists of resection to avoid development of cholangiocarcinoma. The onset of complications such as obstructive jaundice or cholangitis during pregnancy should be treated by percutaneous transhepatic drainage. Two cases of rupture (61,62) and one of 'impending rupture' (63) of choledochal cysts have been described in pregnancy and are clear indications for surgery.

Spontaneous rupture of the common bile duct in pregnancy has also been described (64). The association with pregnancy is likely coincidental.

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