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THE EFFECTS OF PREGNANCY AND FEMALE SEX STEROIDS
ON GALLBLADDER EMPTYING, BILIARY LIPID OUTPUT AND
SMALL BOWEL TRANSIT TIME

by

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SUMMARYTHE EFFECTS OF PREGNANCY AND FEMALE SEX STEROIDS ON GALLBLADDER
EMPTYING, BILIARY LIPID OUTPUT AND SMALL BOWEL TRANSIT TIME

In Western populations gallstones occur in approximately 10 percent of men and 20 percent of women by the age of 65. The majority of gallstones are predominantly composed of cholesterol. The mechanisms leading to cholesterol gallstone formation are poorly understood, but prerequisites include supersaturation of biliary lipids with excess cholesterol, the presence of nucleating factors and the retention of precipitated cholesterol crystals. The greater incidence of gallstones in women is probably related to hormonal factors.

Risk factors in women for gallstone formation include pregnancy and the ingestion of oral contraceptive steroids. The increased probability of gallstones correlates with the number of pregnancies and women who take oral contraceptive steroids or conjugated oestrogens double their risk of developing gallstones. The mechanisms by which pregnancy and oral contraceptive steroids increase the risk of cholesterol gallstones are poorly understood but several mechanisms which include increased biliary cholesterol secretion and retention of precipitated cholesterol crystals have been implicated. A factor contributing to biliary cholesterol saturation in pregnancy may be the observed decrease in the number of enterohepatic cycles during pregnancy. This observation could be caused by slow transit of bile acids through the small intestine, perhaps secondary to progesterone or other neurohormonal effects on small intestinal muscle. Female steroid hormones and pregnancy may also influence gallstone formation by altering the motility of the gallbladder.

The aims of this thesis were to (a) quantitate gallbladder volumes throughout the day in non-pregnant and pregnant subjects as well as in subjects taking oral contraceptive steroids or oestrogens alone, (b) assess the

influence of gallbladder volume and small intestine transit time on biliary lipid composition (c) study lipid composition of gallbladder bile in women taking oral conjugated oestrogens (d) assess oro-caecal transit time in pregnancy and (e) examine the relationship between gastric emptying and gallbladder emptying and time to refilling.

Abdominal ultrasound was used to measure gallbladder volume throughout the day and night and during ingestion of standard meals in pregnant and postpartum women and oral contraceptive users. Results were compared with a control group who were studied in both the follicular and luteal phases of the menstrual cycle. Increases in gallbladder volume in pregnancy were correlated with serum progesterone. Evidence of altered gallbladder motility in pregnancy was found. The gallbladder of pregnancy was sluggish. Fasting volume, the residual volume after meals and the volume remaining in the gallbladder throughout the day doubled during pregnancy and these changes correlated with increases in serum progesterone. In contrast, emptying of the gallbladder was not altered by the phase of the ovulatory cycle or by the ingestion of oral contraceptive steroids. Gallbladder refilling in the day did not occur in normal subjects ingesting three standard meals per day.

The role of the enterohepatic circulation in biliary lipid secretion was studied as this may be an important mechanism by which altered motility of the gallbladder during pregnancy and the ingestion of contraceptive steroids predispose to cholesterol saturated bile and gallstone formation. The rate of biliary secretion was measured in human female volunteers during naso-gastric infusion of both weak and potent stimuli of gallbladder contractility (amino acids and fat respectively) and upper small intestinal bile was simultaneously collected. Changes in the enterohepatic circulation were monitored using abdominal ultrasound to quantify gallbladder volume and breath hydrogen levels after administration of the non-absorbable carbohydrate lactulose to estimate small intestine transit time. Serum levels of

pancreatic polypeptide were measured during each test. Continuous intraduodenal infusion of a solution of amino acids that is known to maximally stimulate pancreatic secretion was less potent in stimulating contraction of the gallbladder than intraduodenal infusion of fat. Bile was relatively more saturated with cholesterol when the gallbladder contracted at a slower rate and the small intestine transit time was slow. The effects of Premarin (Ayerst), a mixture of conjugated oestrogens prepared from the urine of pregnant mares, on gallbladder emptying and biliary lipid secretion in postmenopausal women were studied using the techniques described above. No difference was found in biliary lipid secretion or gallbladder emptying on or off Premarin.

The lactulose breath test was used to measure oro-caecal transit time throughout pregnancy and in the postpartum period. The results were compared with serum progesterone. Oro-caecal transit time was delayed in late pregnancy and returned to normal postpartum. The pattern was similar to the pattern of the sluggish gallbladder of pregnancy suggesting a common neurohormonal mechanism.

To investigate if the rate of emptying of solids from the stomach controlled the rate of gallbladder emptying and time to refilling, the relationship between gallbladder and gastric emptying rates was studied in healthy volunteers. Following the ingestion of a standard radioactively labelled meal gastric emptying was measured scintigraphically while gallbladder volumes were monitored sonographically until gallbladder refilling occurred. The rate of gallbladder emptying in normal volunteers after a regular meal was dependent upon the rate of gastric emptying of the meal. Therefore, some of the delay in gallbladder emptying seen in late pregnancy could be due to delayed gastric emptying.

The findings of this study provide valuable information on normal biliary physiology and a plausible rationale for pregnancy as a gallstone risk factor by demonstrating the presence during gestation of prolonged periods

of gallbladder stasis. The aetiology of this stasis is unlikely to be related to high circulating oestrogen levels and is more likely due to progesterone effects.

Supporting evidence for the latter hypothesis comes from the observation of the lack of influence of exogenous oestrogens on gallbladder and biliary lipid kinetics. The data also suggests that contraceptive steroids are more likely to predispose to cholelithiasis by inducing changes in biliary lipid metabolism rather than changes in gallbladder function.