Supplementary Tables

Supplementary Table 1. Liver and gallbladder findings in women with raised bile acids.

	All women (n=327)
Gallbladder abnormalities	
Gallstones and/or biliary sludge	60 (18.5)
Polyp	12 (3.7)
Cholecystectomy	10 (3.1)
Other*	3 (0.9)
Total	85 (26.2)
Liver abnormalities	
Fatty infiltration	20 (6.1)
Haemangioma†	10 (3.1)
Cyst	3 (0.9)
Other‡	3 (0.9)
Heterogenous echotexture§	2 (0.6)
Total	38 (11.6)

***1 – debris noted in gallbladder, 2 - gallbladder wall thickened, 3 – mild gallbladder oedema.

†In one case haemangioma was picked up in a woman with known Hepatitis C.

‡1 - Small calcific focus, 2 - prior surgical resection, 3 - known focal nodular hyperplasia who had further ultrasound in pregnancy to determine if there was any enlargement.

§In one case heterogenous echotexture was noted in a woman known Hepatitis B who had regular liver ultrasound scans.

Supplementary Table 2. Rates of positive test results comparing between women with severe early-onset disease and those without.

	Severe early-onset disease (peak BA ≥40 µmol/L at <32/40 weeks gestation) n=23	**Non severe early-onset disease n=508**
Hep C IgG	1/21 (4.8)	2/400 (0.5)
Hep B sAg	0/22 (0.0)	7/474 (1.5)
Hep A IgM	0/22 (0.0)	0/368 (0.0)
Smooth Muscle Ab	1/17 (5.9)	4/387 (1.0)
Mitochondrial Ab	1/17 (5.9)	4/386 (1.0)
Liver/kidney microsomal Ab	0/23 (0.0)	0/387 (0.0)
Liver pathology	2/20 (10.0)	36/306 (11.8)
Gallbladder pathology	7/20 (35.0)	78/303 (25.7)

Supplementary Text

Supplementary Text 1

Autoantibody testing for smooth muscle antibodies

404 (76.1%) women were tested for smooth muscle antibodies of whom five (1.2%) were positive: three at 1:80 dilution and two at 1:40. One woman also had Hep-2 ANA antibodies detected at 1:80 dilution. Median liver function test results in these women at time of first raised bile acid were: bilirubin 7 (IQR 4-7) µmol/L, alanine transaminase 104 (IQR 21-186) IU/L, and gamma-glutamyl transferase 31 (15-38) IU/L. Liver function tests (other than bile acid concentrations) were normal during pregnancy in one woman, resolved postpartum in two women, were not checked post-delivery in one woman and remained elevated (62IU/L) at 2 months postpartum in one woman.

Supplementary Text 2

Autoantibody testing for antinuclear antibodies

Hep-2 antinuclear antibody (ANA) testing was performed as part of the ICP investigations at one hospital site only. Of the 227 women tested for Hep-2 ANA, 31 (13.7%) had antibodies detected; 14 at 1:40 dilution, 12 at 1:80 dilution, 3 at 1:160 dilution, 1 at 1:640 dilution and 1 at 1:1280 dilution. Several women had pre-existing autoimmune disease diagnoses including the woman with an ANA titre of 1:1280 who had a diagnosis of fibrotic interstitial lung disease, anti-synthetase syndrome and was also known to be anti-Ro and anti-PL-12 antibody positive. She was not referred for hepatology specialist review as her liver function tests remained in the normal range throughout pregnancy and her raised antibodies were considered to be related to her autoimmune lung disease. Other pre-existing diagnoses in this group of women were sickle cell disease with antiphospholipid syndrome (1:80 dilution), Grave's disease (1:80 dilution) and ulcerative colitis (1:40). On review of electronic health records and clinic letters, no new diagnoses other than ICP were made as a result of testing.

Supplementary Text 3

Autoantibody testing for anti-mitochondrial antibodies

403 (75.9%) women were tested for anti-mitochondrial antibodies, of whom five (1.2%) were positive; three at dilutions of 1:40; one woman tested negative on immunoblot testing, and one woman tested positive on immunoblot testing. Median liver function test results at

time of first raised bile acid were: bilirubin 7 (IQR 7-11) µmol/L, alanine transaminase 47 (IQR 17-330) IU/L, and gamma-glutamyl transferase 17 (14-23) IU/L, Liver function tests other than bile acids were normal throughout pregnancy in one woman. In the four cases that were elevated during pregnancy, three normalised postpartum, and in one case the woman was followed up in primary care (results not available). Three women were referred to gastroenterology services: one was seen by a hepatologist and had liver and biliary magnetic resonance imaging which was normal and no further follow up was arranged, one was seen by a gastroenterologist and discharged, and in the final case the woman that tested positive on immunoblot testing was seen by a hepatologist, had a normal fibroscan and was discharged. In the remaining cases no referrals to specialist services were made and no new clinical diagnoses other than ICP were evident on electronic health records and clinic letters.

Supplementary Text 4

Diagnoses in women presenting with early onset rise in bile acid concentrations

There were 23 women (4.3%) who had a peak bile acid concentration of ≥40 µmol/L at less than 32 weeks' gestation, ten (43.5%) of whom had a peak bile acid concentration of ≥100 µmol/L during pregnancy. In 12/23 cases (52.2%) ICP was the only liver diagnosis during pregnancy with no additional comorbidities of note. In the remaining cases pre-existing comorbidities, alternative explanations for the abnormal liver function tests and/ or additional pregnancy complications were present. In four cases (18.2%), abnormal liver function tests prior to pregnancy, early in pregnancy or postpartum were noted. In one case a woman booked with abnormal liver function but was lost to follow up after delivery, and in one case a woman had a history of abnormal ALT and bilirubin prior to pregnancy with multiple episodes of suspected biliary colic postnatally suggesting gallstone disease rather than ICP. Two women had persistently abnormal LFTs postpartum; one woman was investigated and found to be heterozygous for the ABCB4 genetic variant (Arg1046Ter) and homozygous for the ABCB11 Val444Ala genetic variant and in the other, the woman had not attended for further follow-up. Two women (9.0%) had known inflammatory bowel disease as well as ICP (one case of known Crohn's disease and Primary Sclerosing Cholangitis, one case of known Ulcerative Colitis and Hepatitis C positive), one woman had known seropositive rheumatoid arthritis (and tested positive for anti-mitochondrial antibodies), in

one woman cholestasis could have been triggered by an antibiotic reaction following several courses of antibiotics for pyelonephritis in pregnancy, one woman developed pre-eclampsia and HELLP syndrome, one woman was treated for tuberculosis of the spine during pregnancy but subsequently was diagnosed postpartum with metastatic cancer of unknown primary, and one woman was not diagnosed with ICP but had an episode of gallstone pancreatitis during pregnancy.