may occur,[20] and women with this symptom may have malabsorption of vitamin K. Jaundice is rare, affecting less than 1% of women with ICP,[15] and tends to be mild if it occurs. *[Evidence level 2+]*

The incidence of pre-eclampsia was higher in women with ICP (odds ratio [OR] 3.7 [95% CI 3.2–4.3]): 12.2% of women with ICP had pre-eclampsia compared with 3.4% of women without ICP (228/1876 versus 3385/94 386).[7] As pre-eclampsia can be diagnosed at any gestation from the mid-second trimester, healthcare professionals should ensure that women and pregnant people with ICP receive ongoing blood pressure and urinalysis screening for pre-eclampsia alongside review for ICP.[21] *[Evidence level 1+]*

In a meta-analysis of more than 5000 women with ICP, rates of gestational diabetes were higher in women with ICP (OR 2.4 [95% CI 2.1–2.8]): 13.2% of women with ICP had already been diagnosed with gestational diabetes compared with 5.9% of women without ICP (239/1806 versus 5571/94 384).[7] Additional testing for gestational diabetes is not currently recommended; risk assessment and testing for gestational diabetes should follow national guidelines.[22] *[Evidence level 1+]*

A large Swedish population-based study of 11 388 women with ICP and 113 893 controls found that women who have had ICP had an increased likelihood of later being diagnosed with hepatobiliary disease (hazard ratio (HR) 2.62 [95% CI 2.47–2.77]); 15% in women with ICP versus 6.3% in controls), predominantly due to gallstone disease (HR 2.72 [2.55–2.91]; 11.6% versus 4.6%).[23] However gallstones are common, affecting 5–25% of adults in high income countries,[24] and it is unclear whether gallstone disease predates ICP in such women. *[Evidence level 2–]*

The same study found an association between ICP and immune-mediated diseases later in life (HR 1.28 [1.19–1.38]; 7.2% versus 5.8%). These included diabetes (HR 1.47 [1.26–1.72]; 1.7% versus 1.2%), thyroid disease (HR 1.30 [1.14–1.47]; 2.5% versus 2.0%), psoriasis (HR 1.27 [1.07–1.51]; 1.4% versus 1.1%), inflammatory polyarthropathies (HR 1.32 [1.11–1.58]; 1.3% versus 0.9%) and Crohn's disease (HR 1.55 [1.14–2.10]; 0.4% versus 0.3%), but not ulcerative colitis (HR 1.21 [0.93–1.58]; 0.6% versus 0.5%).[25] Most of these conditions remain at low absolute incidence. The benefit of routine regular screening for these conditions is not proven in women and pregnant people after ICP and is not currently recommended. *[Evidence level 2–]*

Women with ICP have a reported small increased chance of a subsequent diagnosis of other conditions, such as hepatitis C. The UK strategy for hepatitis C detection is based on additional investigations on high-risk groups (e.g. those who have hepatitis B) and does not at present include women with current or previous ICP.[26] In general, after an episode of ICP women do not require additional screening nor follow up.

5.2 | What is the risk of stillbirth?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Advise women with isolated ICP and a singleton pregnancy that the risk of stillbirth only increases above population rate once their serum bile acid concentration is 100 micromol/L or more: • **In women with peak bile acids 19–39 micromol/L and no other risk factors, advise them that the risk of stillbirth is similar to the background risk.** • **In women with peak bile acids 40–99 micromol/L and no other risk factors, advise them that the risk of stillbirth is similar to the background risk until 38–39 weeks' gestation.** • **In women with peak bile acids 100 micromol/L or more, advise them that the risk of stillbirth is higher than the background risk**	1+	A	Demonstrated in the meta-analysis of 23 studies.
Advise women with ICP that the presence of risk factors or co-morbidities (such as gestational diabetes and/or pre-eclampsia and/or multifetal pregnancy) appear to increase the risk of stillbirth and may influence decision-making around timing of planned birth	2+ to 2–	D	Reported in retrospective cohort studies
Advise women with ICP and a twin pregnancy that the risk of stillbirth is higher compared with a twin pregnancy without ICP	2–	D	Reported in a retrospective cohort study from China.

Stillbirth remains the major concern for women and pregnant people with ICP and for their healthcare practitioners. A large systematic review and individual patient data meta-analysis of women with ICP reported that, for singleton pregnancies, the risk of stillbirth only increased above population rate once serum bile acid concentrations were 100 micromol/L or more (Table 2).[7]

The national stillbirth rates from 28 weeks' gestation for 2015 for countries contributing to these ICP data varied from 0.18% to 0.72% depending on country; the UK stillbirth rate was 0.29%.[7]

The pathophysiology of stillbirth in ICP is uncertain, but it is thought that bile acids may cause an acute fetal anoxic event possibly due to fetal arrhythmia[27] or acute placental

TABLE 2 Association between peak bile acid concentration and prevalence of stillbirth in singleton pregnancy (adapted from Ovadia et al.)[7]

	Peak bile acid concentrations	Prevalence of stillbirth (with 95% CI)	Absolute numbers of stillbirths	Hazard ratio (with 95% CI)
National UK stillbirth rate from 28 weeks (2015)	–	0.29%[a]	–	–
Mild ICP	Raised bile acids 19–39 micromol/L	0.13% (0.02–0.38%)	3/2310	Referent
Moderate ICP	40–99 micromol/L	0.28% (0.08–0.72%)	4/1412	2.35 (0.52–10.50) $p = 0.2642$
Severe ICP	≥100 micromol/L	3.44% (2.05–5.37%)	18/524	30.50 (8.83–105.30) $p < 0.0001$

[a]95% confidence intervals not given.

vessel spasm.[28] In singleton pregnancies, stillbirth was associated with peak total bile acid concentration but not with alanine transaminase.[7] *[Evidence level 1+]*

A 12-month UK Obstetric Surveillance System (UKOSS) study in 2010–2011 reviewed 669 cases of ICP in singleton pregnancy with bile acids 40 micromol/L or more across the UK which included 10 stillbirths.[29] Of these, seven had coexistent pregnancy complications (three had gestational diabetes; two had pre-eclampsia; two had non-specified complications). These differences remained significant against national data and suggest that women with ICP and other comorbidities warrant additional surveillance. *[Evidence level 2+]*

The aetiology of adverse perinatal outcomes, including stillbirth, in multifetal pregnancies is multifactorial. The risk of stillbirth in multifetal pregnancies is higher than in singleton pregnancies.[30] *[Evidence level 2–]*

One retrospective cohort study from China specifically evaluated ICP in twin pregnancies.[31] They reviewed 129 twin pregnancies complicated with ICP and 1793 twin pregnancies without ICP (2006–2014). There was an increased risk of stillbirth in twin pregnancies with ICP compared with twin pregnancy without ICP (3.9% versus 0.8%, aOR 5.75 [95% CI 2.00–16.6]). This was further stratified as a stillbirth risk of 3.3% in women with bile acids of 10–39 micromol/L and 5.1% in women with bile acids of 40 micromol/L or more. Stillbirths with ICP in twin pregnancies occurred between 33–35 weeks' gestation, compared to 36–38 weeks' gestation among singletons. *[Evidence level 2–]*

5.3 | What is the risk of perinatal morbidity?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Advise women with moderate or severe ICP that they have a higher chance of both spontaneous and iatrogenic preterm birth	**1+**	**A**	Demonstrated in the meta-analysis of 23 studies
Advise women with moderate or severe ICP that they have an increased chance of having meconium stained amniotic fluid during labour and birth	**1+**	**A**	Demonstrated in the meta-analysis of 23 studies
Advise women with moderate or severe ICP that their baby is more likely to receive neonatal care	**1+**	**A**	Demonstrated in the meta-analysis of 23 studies

In the meta-analysis of more than 5000 women with ICP, women with bile acids ≥40 micromol/L had an increased overall risk of both spontaneous preterm birth (OR 3.47 [95% CI 3.06–3.95]) and iatrogenic preterm birth (OR 3.65 [1.94–6.85]),[7] the latter likely reflecting the policy of 'active management' with planned early birth (despite a limited evidence base for this approach).[32] The percentage of women with singleton pregnancies who gave birth before 37 weeks increased with increasing bile acid concentration: 16.5% of women with bile acids below 40 micromol/L (373/2264), 19.1% of women with bile acids 40–99 micromol (261/1368), and 30.5% of women with bile acids 100 micromol/L or more (157/514). The majority of multifetal pregnancies were born preterm.[7] *[Evidence level 1+]*

In the same meta-analysis of more than 5000 women with ICP, there was an increased chance of meconium stained amniotic fluid (of any grade) in women with ICP: OR 2.60 (95% CI 1.62–4.16).[7] The 2010–2011 UKOSS study of 713 women with bile acids 40 micromol/L or more found that these women had meconium stained amniotic fluid at lower gestational ages, and more commonly at 35–38 weeks, when compared with women without ICP.[29] The presence of meconium stained amniotic fluid in labour should be managed using national guidance.[33] *[Evidence level 1+]*

ICP is associated with a small increase in admission to the neonatal unit: OR 1.47 (95% CI 1.03–2.10).[7] There was, however, no difference in the rate of a neonatal 5 min Apgar score of less than 7,[7] (which is associated with increased

neonatal morbidity and mortality): OR 1.41 (0.95–2.10).[34,35] *[Evidence level 1+]*

The 2010–2011 UKOSS study on 713 UK women with ICP (bile acids 40 micromol/L or more) showed that 45% of neonatal admissions were due to preterm birth, and 30% due to respiratory problems.[29] Their study had a preterm birth rate of 25%, with a 15% rate of meconium stained liquor, but no cases of meconium aspiration. The median duration of stay in the neonatal unit was 7 days (IQR 2.25–13.75 days).[29] *[Evidence level 1+]*

6 | HOW SHOULD WOMEN WITH ICP BE MONITORED?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Review women with ICP within a consultant-led maternity unit	**4**	**GPP**	Women with ICP may be at increased likelihood of pregnancy complications

The frequency and content of monitoring for women and pregnant people with ICP should be determined in conjunction with the woman or pregnant person and based on the amount of discomfort or distress they experience, bile acid concentrations, gestational age and the presence of other morbidities. This might incorporate review of diagnosis, discussion of maternal and fetal wellbeing, treatment of pruritus, and need for further biochemical testing. *[Evidence level 4]*

6.1 | What maternal monitoring should be advised?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
For women with ICP, consider repeating liver function tests and bile acids after 1 week, and then determine frequency on an individual basis	**4**	**D**	Due to the unpredictable nature of ICP, it is good practice to offer monitoring

Maternal itch appears to be poorly correlated to the level of biochemical abnormality. For women with ICP, ongoing monitoring of symptoms and biochemical monitoring may show:

- rising bile acid concentrations, and if 100 micromol/L or more, the diagnosis of severe ICP,
- fall in bile acids concentrations into a more reassuring category, such that frequency of monitoring and/or care can be altered accordingly,
- spontaneous resolution of itch and biochemical abnormalities returning to normal levels, in which case the diagnosis should be reconsidered [see above in Section 4.1],
- Fluctuating bile acid concentrations but peak concentrations within the boundaries for their current diagnosis. *[Evidence level 4]*

All women with itch and an initial raised bile acid level, should have a second bile acid measurement repeated around 1 week later before any diagnostic or care decisions are determined, as it is common for women with bile acid levels over 100 micromol/L and 40–100 micromol/L to have subsequent bile acid concentrations that are much lower.[8]

The subsequent frequency at which women and pregnant people have biochemical assessment will be determined on an individual basis and according to the impact that the result might have on further care (see Section 8.1):

- If the woman has mild ICP with peak bile acids 19–39 micromol/L, they could have weekly testing as they approach 38 weeks' gestation in order to inform timing of birth.
- If the woman has moderate ICP with peak bile acid 40–99 micromol/L, especially if they are approaching 35 weeks' gestation, weekly testing should be considered, as timing of birth may be influenced if levels rise to 100 micromol/L or more.
- If the woman has severe ICP with peak bile acid 100 micromol/L or more, further routine testing of bile acids might not impact on decision making and therefore may not be routinely required. *[Evidence level 4]*

6.2 | What fetal monitoring should be advised?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Clinicians should be aware that fetal ultrasound and/or cardiotocography (CTG) do not predict or prevent stillbirth in ICP	**3**	**D**	Several case studies describe fetal death despite close CTG and/or ultrasound surveillance
Advise women with ICP to monitor fetal movements and present for immediate assessment at their local maternity unit if they have any concerns	**4**	**D**	Recommended in Saving Babies' Lives Care Bundles version 2 (2019) for all pregnant women

In ICP, there is evidence that cardiotocography (CTG) monitoring or biophysical profile do not predict stillbirth. Several studies describe fetal death despite close surveillance and previously normal ultrasound scans (including fetal Doppler measurements), biophysical profile, and/or CTG monitoring.[31,36,37,38] *[Evidence level 3]*

ICP is not associated with fetal growth restriction, with no difference in birthweight centiles compared with babies born to women without ICP,[7] and therefore strategies for antenatal monitoring for placental insufficiency are unlikely to be beneficial in women with isolated ICP. *[Evidence level 3]*

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All pregnant women and pregnant people should be advised to monitor the quality and quantity of their fetal movements, and report any reduction or change to their local maternity unit immediately, as recommended in national guidance. [1] Maternal detection of movements is simple and not time consuming for women or staff, but its specific role in monitoring pregnancies complicated by ICP has not been assessed. *[Evidence level 4]*

7 | WHAT IS THE ROLE OF DRUG TREATMENT IN THE TREATMENT OF ICP?

7.1 | What impact on maternal symptoms (itch), maternal biochemistry and fetal outcome can be expected?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Advise women that there are no treatments that improve pregnancy outcome (or raised bile acid concentrations) and treatments to improve maternal itching are of limited benefit	**1+**	**A**	Systematic review has shown no clear evidence of maternal or perinatal benefit with treatments to reduce itching or adverse perinatal outcomes

The role of drug treatment in ICP is to try to reduce maternal itching (which may be of variable intensity and is unrelated to bile acid concentrations). There is no evidence that routine medical treatment improves maternal raised bile acid concentrations or perinatal outcomes.[39] *[Evidence level 1+]*

Topical emollients

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Consider topical emollients such as aqueous cream (with or without menthol added) to ameliorate skin symptoms	**4**	**D**	Used in clinical practice, but not formally evaluated for evidence of benefit in reducing itching

Although there is minimal high-quality evidence to endorse topical emollient treatment in women with ICP and it is not a disease-modifying drug, there is consensus that such treatment may relieve some of the discomfort associated with itching and has no known harmful effects. *[Evidence level 4]*

Antihistamines

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Consider antihistamine agents, such as chlorphenamine, particularly at night although the effectiveness of this treatment is uncertain in women with ICP	**4**	**GPP**	Used in clinical practice, but not formally evaluated for evidence of benefit in reducing itching

Chlorphenamine has antihistamine properties and may have sedative side-effects in some women. The effectiveness of the treatment is uncertain in women and pregnant people with ICP, and relief may be more related to its sedative action than a direct effect. There is experience of using chlorphenamine in other conditions in pregnancy (such as hay fever) and harmful effects have not been reported. Other common antihistamine agents including loratadine and cetirizine are also used in pregnancy for other indications but do not have sedative side-effects. *[Evidence level 4]*

Ursodeoxycholic acid

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Do not routinely offer ursodeoxycholic acid for the purpose of reducing adverse perinatal outcomes in women with ICP	**1+**	**A**	The largest randomised controlled trial of ursodeoxycholic acid showed no evidence of significant benefit

Evidence from randomised controlled trials shows that there is no reduction in adverse perinatal outcomes in women prescribed ursodeoxycholic acid, compared to women in the placebo group.[39,40] No sub-group (e.g. based on maternal bile acid concentrations, or gestational age at presentation) was identified that might benefit. *[Evidence level 1+]*

There is a small (around 5 mm, on a linear 0 to 100 mm itch scale with 0 'no itch' and 100 'worst imaginable itch') reduction in maternal itch in women taking ursodeoxycholic acid.[39] Women and clinicians considered that a reduction of at least 30 mm on the itch scale would be clinically relevant and worthwhile;[40] the majority of women would therefore not consider this a useful treatment. It remains possible that some women's and pregnant people's itching may reduce with ursodeoxycholic acid, but it is not clear how such women might be identified. A recent secondary analysis of the largest trial could not identify a cohort based on bile acid

concentration or itch score who would benefit.[8] *[Evidence level 1+]*

A systematic review and individual participant meta-analysis of ursodeoxycholic acid in ICP included four randomised controlled trials of over 800 women (of whom 183 had bile acid of 40 micromol/L or more) with a primary outcome of stillbirth and a composite secondary outcome of stillbirth and preterm birth.[41] Ursodeoxycholic acid had no impact on the primary endpoint. Spontaneous preterm birth under 34 weeks' gestation was not reduced (5/387 women taking ursodeoxycholic acid versus 6/366 women taking placebo, aOR 0.75, 95% CI 0.23–2.51, $p = 0.65$). Spontaneous preterm birth under 37 weeks' gestation was reduced in women taking ursodeoxycholic acid compared with placebo (18/387 versus 32/366 aOR 0.46, 95% CI 0.25–0.86, $p = 0.015$).

In women with bile acid concentrations 40 micromol/L or more who are 34–36 weeks' gestation, ursodeoxycholic acid may offer some benefit in reducing late preterm birth. However, as with other circumstances where preterm birth occurs[42] it is not clear that this reduction results in any benefit to the baby. The optimal starting gestation and dosing regimen are unclear. Some women and pregnant people with bile acid concentrations of 40 micromol/L or more may wish to take ursodeoxycholic acid with a view to prolonging gestation, but as this does not prevent stillbirth, the advantage of doing so may be less clear, especially for those with bile acids over 100 micromol/L.

In the largest trial, maternal bile acid concentrations were found to be higher in the group treated with ursodeoxycholic acid,[39] possibly as a result of standard laboratory assays being unable to distinguish between endogenous and exogenous sources. Ursodeoxycholic acid cannot therefore be recommended for the purpose of reducing this biochemical marker of disease. In the same trial, women treated with ursodeoxycholic acid had lower alanine transaminase levels than those taking placebo, but the clinical implications of this are uncertain, as alanine transaminase levels have no association with stillbirth.[7] *[Evidence level 1+]*

Other agents

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Do not offer other agents for treatment of ICP outside of a research study or individualised specialist treatment	**3**	**D**	In the absence of evidence of benefit, routine use of other treatments is not recommended

Use of rifampicin has been reported largely in single cases[43] and by questionnaire survey of affected women,[44] but there is no evidence from randomised controlled trials to support its routine use in ICP. Further research is underway to evaluate its use in women with ICP.[45] In women and pregnant people with early-onset severe disease, an opinion from a specialist in ICP should be sought before considering rifampicin treatment. *[Evidence level 3]*

7.2 | Is there a place for vitamin K use?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Consider maternal vitamin K treatment only if there appears to be reduced absorption of dietary fats (e.g. presence of steatorrhoea) and/or evidence of abnormal prothrombin time if coagulation studies are performed	**4**	**D**	Extrapolation from other clinical scenarios where dietary fat absorption is impaired, but routine use in all women with ICP is lacking an evidence base

The experience of experts is that the large majority of women with ICP will not have evidence of reduced fat absorption[9] and routine use of vitamin K treatment is not indicated. If women have symptoms such as steatorrhoea,[20] coagulation assessment should be performed and use of vitamin K treatment considered (prescribed as a water-soluble formulation such as menadiol sodium phosphate at a dose of 10 mg daily). *[Evidence level 4]*

8 | HOW SHOULD WOMEN BE ADVISED ON TIMING AND MODE OF BIRTH?

8.1 | Timing of birth

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Consider options of planned birth by 40 weeks' gestation or ongoing antenatal care according to national guidance in women with mild ICP (peak bile acids 19–39 micromol/L) and no other risk factors; advise women that the risk of stillbirth is similar to the background risk	**1+**	**A**	Systematic review with individual patient data meta-analysis reporting risk of stillbirth, stratified by peak maternal bile acid concentration