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RCOG GREEN-TOP GUIDELINES

Intrahepatic cholestasis of pregnancy

Green-top Guideline No. 43 June 2022

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This is the third edition of the guideline. The first edition was published in 2006 and the second in 2011 under the title *Obstetric Cholestasis*.

Key recommendations

- The diagnosis of intrahepatic cholestasis of pregnancy (ICP) should be considered in pregnant women who have itching in skin of normal appearance and raised peak random total bile acid concentration of 19 micromol/L or more. [Grade D]
- Additional laboratory and/or imaging investigations are not recommended unless itch is associated with atypical clinical symptoms, the presence of relevant comorbidities, or in early onset severe ICP. Consider additional postnatal investigations in women in whom resolution of abnormal liver function tests is delayed or does not occur. [Grade C]
- Consider discussing the care of women with severe, very early or atypical presentation of what appears to be ICP with a hepatologist. [Grade D]
- Confirm the diagnosis of ICP in the postnatal period at least 4 weeks after birth, with resolution of itching and liver function tests returning to normal (including bile acids). [Grade D]
- 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 (mild ICP) and no other risk factors, advise them that the risk of stillbirth is similar to the background risk. Consider options of planned birth by 40 weeks' gestation or ongoing antenatal care according to national guidance.
  - In women with peak bile acids 40–99 micromol/L (moderate ICP) and no other risk factors, advise them that the known risk of stillbirth is similar to the background risk until 38–39 weeks' gestation. Consider planned birth at 38–39 weeks' gestation.
  - In women with peak bile acids 100 micromol/L or more (severe ICP), advise them that the risk of stillbirth is higher than the background risk. Consider planned birth at 35–36 weeks' gestation. [Grade A]
- Advise women with ICP and a twin pregnancy that the risk of stillbirth is higher compared with a twin pregnancy without ICP. [Grade D]
- Clinicians should be aware that fetal ultrasound and/or cardiotocography (CTG) do not predict or prevent stillbirth in ICP. [Grade D]

- 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. [Grade D]
- 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. [Grade A]
- Do not routinely offer ursodeoxycholic acid for the purpose of reducing adverse perinatal outcomes in women with ICP. [Grade A]

1 | PURPOSE AND SCOPE

This guideline summarises the evidence regarding the diagnosis, and the maternal and fetal risks of intrahepatic cholestasis of pregnancy (ICP), previously called obstetric cholestasis. It provides guidance regarding the different care options available. These should be considered in conjunction with the wishes of the woman, as part of shared and informed decision-making.

While some high quality randomised controlled trials in ICP have now been completed, many publications do not have such a rigorous design, and this limits the ability to provide detailed evidence-based recommendations for specific aspects of care. Areas of uncertainty are highlighted along with recommendations for future research in this field.

Within this document we use the terms pregnant woman and women's health. However, it is important to acknowledge that it is not only people who identify as women for whom it is necessary to access care. Obstetric and gynaecology services and delivery of care must therefore be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth.

2 | INTRODUCTION

The care of women and pregnant people with ICP is driven by concern from women and from healthcare professionals over the potential increased risk of stillbirth. Reduction of stillbirth is a priority in maternity care in the UK.[1]

Prevalence is influenced by genetic and environmental aspects and varies between populations. In the UK, ICP affects 0.7% of pregnancies in multi-ethnic populations, and 1.2%–1.5% of women of Indian-Asian or Pakistani-Asian origin.[2,3]

Intrahepatic cholestasis of pregnancy is a multifactorial condition. It is characterised by pruritus in the absence of a primary skin condition, with abnormal maternal bile acid concentrations. The onset of symptoms is most common in the third trimester, but can be earlier in pregnancy.[4] Alternative diagnoses (such as pre-eclampsia) should always be considered before a diagnosis of ICP is made; it is also possible for other conditions to co-exist. Pruritus and raised bile acid concentrations should return to normal after birth.

Ideally, all women with ICP should have liver function tests (including bile acids) checked after birth, as a proportion may have persistent abnormalities suggestive of additional or alternative comorbidities (such as non-alcoholic fatty liver). Few studies have reported comprehensive postnatal follow-up of women to assess for additional diagnoses.

There are no clinical features or laboratory patterns that are unique to ICP, as other conditions can cause itching, or raised bile acid concentrations in pregnancy. Around 25% of pregnant women develop itching[2,5]; the majority of these do not have and do not develop ICP.

Historically, ICP has been diagnosed in women on the basis of self-reported itching together with elevation of any of a wide range of liver function tests beyond pregnancy-specific limits.[6] There is now increasing evidence that in singleton pregnancies, most liver function tests do not reflect risk of fetal demise and that only maternal total bile acid concentrations results are associated with the risk of stillbirth.

A meta-analysis of 23 studies involving 5557 women with ICP and 165 136 healthy controls, and the first individual patient data analysis of 5269 women with ICP from 27 studies[7] has been published since this guideline was last updated. In singleton pregnancies, stillbirth was associated with maximum total bile acid concentration, especially over 100 micromol/L. In pregnancies with co-morbidities that themselves may impact on pregnancy outcome (such as multifetal, diabetic, pre-eclamptic pregnancies), these must be taken into account when considering risks and care options.

Bile acid concentrations are not associated with intensity of itching.[8] Other liver blood tests, such as alanine transaminase or aspartate transaminase are not associated with pregnancy outcome.[7] In light of this, the consensus is now that the diagnosis of ICP requires elevated maternal bile acid concentrations, and that women and pregnant people with itching and isolated raised transaminases alone (with normal bile acid concentrations) should not be given a diagnosis of ICP.[9] This is supported by the recent systematic review described above, in which there was no association between abnormal maternal transaminase concentrations and stillbirth.[7]

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2.1 | What terminology should be used to describe the conditions?

Most published studies to date have included women with ICP diagnosed on the basis of itch and elevated bile acids above the laboratory reference range. In a study of 560 women a pregnancy specific reference range for non-fasting bile acids was calculated with an upper limit of normal of 18 micromol/L.[10] In light of the meta-analysis and individual patient data analysis showing that stillbirth risk is not linked with alanine transaminase levels, but is linked with peak bile acid concentration,[7] the suggested terminology for pregnant women with otherwise unexplained itching is outlined in Table 1.

2.2 | What are the clinical issues for women with ICP?

The clinical issues for women and pregnant people with ICP may include coping with the itching, monitoring options during the pregnancy, options for controlling maternal symptoms, reducing fetal risk, preterm birth, difficulty sleeping, anxiety about the condition, and optimal timing of birth. Itching varies in nature between different women and for some women at different times, from mild to unbearable and from focal to widespread, and for some women this can have an adverse impact on their mental wellbeing. Liver failure (impaired synthetic function such as prolonged prothrombin time, or metabolic dysfunction such as hypoglycaemia) is not a typical feature of ICP.

3 | IDENTIFICATION AND ASSESSMENT OF EVIDENCE

The Cochrane Library and electronic databases (DARE, EMBASE, Trip, MEDLINE and PubMed) were searched looking for the following terms in the title or abstract 'cholestasis', 'intrahepatic cholestasis', 'obstetric cholestasis', 'bile acids and salts' and 'liver function test'. The search was restricted to articles published until August 2017. The full search strategy is available to view online as supporting information. A further search was undertaken up to February 2021 and additional articles included as appropriate. The full literature search is available to view online as supporting information (Appendices S1 and S2).

This Royal College of Obstetricians and Gynaecologists (RCOG) guideline was developed in accordance with the standard methodology for producing RCOG Green-top Guidelines.[11]

TABLE 1 Terminology for pregnant women with itching of normal skin

Diagnosis	Clinical features
Gestational pruritus	Itching and peak bile acid concentrations <19 micromol/L[a]
Mild ICP	Itching and raised peak bile acid concentrations 19–39 micromol/L
Moderate ICP	Itching and raised peak bile acid concentrations 40–99 micromol/L
Severe ICP	Itching and raised peak bile acid concentrations ≥100 micromol/L

Note: Peak bile acid concentrations refer to the highest bile acid concentration recorded during a woman's pregnancy. Thus a woman's diagnosis may progress in severity during pregnancy.

[a]The upper limit of normal bile acid concentrations in pregnancy is 18 micromol/L.[10]

4 | HOW IS ICP DIAGNOSED?

4.1 | How should the diagnosis of ICP be made?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
The diagnosis of ICP should be considered in pregnant women who have itching in skin of normal appearance and raised peak random total bile acid concentration of 19 micromol/L or more. The diagnosis is more likely if it is confirmed that itching and raised bile acids resolve after birth	**4**	**D**	There is no diagnostic test for ICP, but this definition is pragmatic, and is used in clinical research involving women with ICP
If a diagnosis of ICP is suspected, carry out a structured history and examination, so that other causes of itching and liver dysfunction can be excluded	**4**	**D**	There are other potential causes of itching and abnormalities of liver function tests in pregnant women
Offer repeat liver function tests and bile acid measurement (depending on gestation and clinical context) in women with normal blood results whose itch persists, and no other cause is apparent	**4**	**D**	Women and pregnant people with gestational pruritus may develop ICP up to 15 weeks after initial presentation
If resolution of itching is associated with normalisation of bile acids and liver function tests during pregnancy, the diagnosis of ICP is unlikely to be correct	**4**	**D**	In clinical practice, diagnoses should be reconsidered if the clinical presentation changes

New onset pruritus in pregnant women, if associated with rash is unlikely to be ICP. If the itchy skin looks abnormal (other than excoriations) then another cause should be considered. Liver function tests and bile acids are not required routinely. Clinicians should be aware however, that skin conditions (e.g. eczema) and ICP can co-exist.

If the itchy skin looks normal, or there is only skin trauma due to scratching, the diagnosis may include gestational pruritus, or ICP (see Table 1); measurement of bile acid concentrations and liver function tests should be undertaken. Raised bile acid concentration of 19 micromol/L or more in pregnancy supports a diagnosis of ICP. *[Evidence level 4]*

When clinically indicated, bile acid measurements should be taken at a convenient time, and do not need to be performed fasting. By taking a non-fasting upper limit of normal up to 19 micromol/L for bile acid concentrations, almost 20% of women previously considered to have ICP (as their bile acid concentrations are below 19 micromol/L but above the standard laboratory cut off) do not have this diagnosis. Published data indicate that pregnant women with raised bile acids less than 19 micromol/L are not at increased risk of stillbirth.[10] In addition, as prandial readings are higher than fasting, this approach maximises the chance of detecting peak bile acid readings that are of greater clinical importance for preventing adverse pregnancy outcome.

Itching of normal skin, liver dysfunction and elevated bile acid concentrations are non-specific and have a wide range of causes. A healthcare professional should carry out a structured history and examination, and consider other potential diagnoses: these may be pregnancy specific (including pre-eclampsia) or coincidental to the pregnancy (comprehensively reviewed by Walker et al).[12] Drug reactions, allergic reactions, and urticaria should form part of the differential diagnosis. *[Evidence level 4]*

In women and pregnant people with persistent itch of normal skin and normal blood results, an initial diagnosis of gestational pruritus should be considered. Women can go on to develop ICP up to 15 weeks after a diagnosis of gestational pruritus.[13] If itching continues for these women, they should be offered review with repeated liver function tests and bile acid measurement as clinically indicated. The frequency and duration of review and tests should be determined on an individual basis, but might be based around scheduled care. The gestational age is also relevant in determining test frequency, particularly later in the third trimester when a diagnosis of ICP may change care around the timing of birth (aiming to reduce the risk of stillbirth) [see Section 5.2]. Use pregnancy-specific reference ranges for liver function tests.[6] *[Evidence level 4]*

Pruritus and biochemical abnormalities usually persist throughout pregnancy in women with ICP, although it is very common for them to fluctuate. However, in a few women, pruritus and biochemical abnormalities will resolve completely for the remainder of the pregnancy; clinicians may then need to reconsider the cause of the original symptoms and why resolution has occurred. There are many causes of transient liver function test abnormalities, such as drug reactions (e.g. to antibiotics) or non-specific viral illnesses. When resolution occurs during pregnancy, it is unlikely that the original diagnosis was correct. In discussion with the woman or pregnant person, ongoing care can usually return to normal, and decisions about timing of birth should be based on usual obstetric practice, although there should be greater caution if bile acid concentrations have been markedly raised (e.g. 100 micromol/L or more). *[Evidence level 4]*

4.2 | What is the role of other investigations in the care of women with suspected ICP?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Additional laboratory and/or imaging investigations are not recommended in every woman, but could be considered on an individual basis. Consider antenatal testing only if there are atypical clinical symptoms, presence of relevant comorbidities, or early onset severe ICP. Consider postnatal investigations in women in whom resolution of abnormal liver function tests is delayed or does not occur	2+	C	A cohort study showed that the likelihood that routine investigations would identify other causes of the clinical picture was extremely low

Previous RCOG guidelines[14] have recommended routine laboratory and imaging investigations to exclude other causes for the clinical picture of ICP, including viral and autoimmune tests and liver ultrasound. A recent retrospective review of over 500 pregnant women with raised bile acid concentrations suggests that the likelihood of identifying a viral, autoimmune, or structural cause for the itching and liver derangement that was not suspected on other clinical grounds is extremely low as no new diagnoses were made following investigations.[15] Therefore, routine use of other investigations is no longer recommended. The UK National Screening Committee does not recommend routine screening for hepatitis C in pregnancy due to lack of evidence of benefit[16]; the same uncertainties apply to pregnant women with ICP. Routine hepatitis C testing is therefore not currently recommended in women with suspected or proven ICP. Additional investigations (including for hepatitis C) should be considered in women and pregnant people with an atypical or uncertain picture of ICP. This may include women with markedly elevated transaminases, early onset of ICP in the first or second trimester, a rapidly progressive biochemical picture, any features of liver failure or evidence of acute infection, or if resolution does not occur after birth. *[Evidence level 2+]*

Three cohort studies of 223 women,[17] 531 women[15] and 745 women[18] with ICP who had routine coagulation testing reported no cases of prolonged prothrombin time in women with uncomplicated clinical presentations. The small number of abnormal results were in women with alternative diagnoses (such as acute fatty liver of pregnancy). Coagulation testing is therefore not recommended routinely for women and pregnant people with uncomplicated ICP. It should be considered on an individual basis especially when failure of liver synthetic function or failure of fat absorption is suspected. *[Evidence level 2+]*

4.3 | When should specialist hepatology advice be sought?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Consider discussing the care of women with severe, very early or atypical presentation of what appears to be ICP with a hepatologist	**4**	**D**	It is good practice to discuss complex or unusual cases with relevant specialists

Women who develop pruritus and abnormalities in liver function and bile acids in the first or second trimester and especially in the first trimester are more likely to have an underlying genetic predisposition or an alternative or additional diagnosis. Input from a hepatologist and/or a clinician with a special interest in cholestasis to discuss investigations and treatment options should be considered. A postnatal referral should also be considered for women and pregnant people who do not have resolution of itch and biochemical abnormalities after birth. *[Evidence level 4]*

4.4 | What is the usual postnatal resolution?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Confirm the diagnosis of ICP in the postnatal period at least 4 weeks after birth, with resolution of itching and liver function tests returning to normal (including bile acids)	**4**	**D**	It is good practice to ensure that women with ICP have appropriate follow up

For many women with ICP, itching will stop very soon after birth; in the majority it stops in the first few hours or days.

Liver function tests are non-specific and can become abnormal during birth. Alanine transaminase and aspartate transaminase are found in smooth muscle, breast and red blood cells and may be elevated for other reasons in the immediate post-partum period. *[Evidence level 4]*

Women with ICP who have no other diagnoses are usually clinically well; liver function tests and bile acids should not be measured until at least 4 weeks after birth, to allow time for levels to return to a normal range.[19] If the woman or pregnant person is clinically unwell, other or additional diagnoses should be suspected and liver function testing should be repeated sooner, as clinically indicated. *[Evidence level 4]*

5 | MATERNAL AND PERINATAL RISKS

5.1 | What is the maternal morbidity?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Advise women with ICP that the predominant symptom is itching. This can be severe, may fluctuate and may markedly affect sleep	**2+**	**C**	It is usual clinical practice to discuss symptoms with women
Women with ICP may have a higher chance of developing pre-eclampsia or gestational diabetes. They should have blood pressure and urine monitoring, and testing for gestational diabetes according to national guidance	**1+**	**B**	It is important that women with ICP continue to have normal aspects of antenatal care

Itching is the main symptom of ICP. The itching is not specific to any single location; it is often generalised and may affect the palms of the hands and/or the soles of the feet; it ay vary in intensity.[2] For women and pregnant people with gestational pruritus or ICP, there is poor correlation between severity of itch and level of bile acids,[8] and regardless of the diagnosis, itch can be very severe for some women and may negatively impact their emotional wellbeing and mental health. The itching is often more pronounced at night, which can interfere with sleep. *[Evidence level 2+]*

Additional symptoms of cholestasis, such as dark urine and pale stools, are infrequently reported.[4] Steatorrhoea

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

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Recommendation	Evidence quality	Strength	Rationale for the recommendation
Consider planned birth at 38–39 weeks' gestation in women with moderate ICP with peak bile acids 40–99 micromol/L and no other risk factors; advise them that the overall risk of stillbirth is similar to the background risk until 38–39 weeks' gestation	**1+**	**A**	Systematic review with individual patient data meta-analysis reporting risk of stillbirth, stratified by peak maternal bile acid concentration
Consider planned birth at 35–36 weeks' gestation in women with severe ICP with peak bile acids 100 micromol/L or more; advise them that the risk of stillbirth is higher than the background risk	**1+**	**A**	Systematic review with individual patient data meta-analysis reporting risk of stillbirth, stratified by peak maternal bile acid concentration
Advise women that the presence of co-morbidities (such as gestational diabetes, pre-eclampsia, multifetal pregnancy) appear to increase the risk of stillbirth and may influence decision-making around timing of planned birth	**2+**	**C**	Evidence from national surveillance case control study supported by other case series demonstrating increased stillbirth risk with comorbidities

Active care in ICP, usually referring to planned birth around 38 weeks' gestation, came into practice in many settings, including the UK, despite inadequate evaluation of its benefit or an understanding of which women with ICP might be at increased risk of adverse perinatal outcomes. Previous studies had reported on cohorts of women with ICP, often after introduction of active care, and speculated that low stillbirth risk is related to such a policy,[46,47] but few had evaluated prognostic factors to allow better stratification to tailor timing of birth. *[Evidence level 1+]*

A large systematic review and individual patient data meta-analysis of women with ICP has reported that the risk of stillbirth is 0.13% in women with peak bile acids less than 40 micromol/L, which is not higher than background population risk.[7] Although the risk of stillbirth remains low throughout gestation for these women, the benefits of continuing the pregnancy after 40 weeks' gestation may be outweighed by the risk, therefore it is reasonable to discuss with the woman or pregnant person whether they wish to continue the pregnancy or have a planned birth. *[Evidence level 1+]*

The risk of stillbirth in women with peak bile acids of 40–99 micromol/L was 0.28%. This was not higher than overall background population risk,[7] but did appear to increase at around 38–39 weeks' gestation. Although the number of affected pregnancies is small and the confidence intervals wide, it is reasonable to offer planned birth at this gestation for women and pregnant people with peak bile acids of 40–99 micromol/L, or earlier if other comorbidities (such as gestational diabetes or pre-eclampsia) are present. *[Evidence level 1+]*

For women with peak bile acids 100 micromol/L or more, the risk of stillbirth is 3.44%, which is higher than background population rate, and the risk appears to increase from 35–36 weeks' gestation. This information should be shared with the woman or pregnant person and planned birth considered, based on other factors and the woman's preferences. This is in keeping with other studies using different methodologies, including a retrospective cohort study of 1 604 386 pregnancies assessing composite perinatal mortality risk[48] and a decision modelling study concluding that 36 weeks' gestation was optimal.[49] *[Evidence level 1+]*

In women with ICP and peak bile acids 40 micromol/L or more, co-morbidities may be associated with a greater risk of stillbirth.[29] The presence of and risks related to co-morbidities should be taken into account when considering the timing of planned birth. *[Evidence level 1+]*

8.2 | Mode of birth

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Advise women that ICP in itself does not impact their choice around mode of birth and that these decisions should be based on usual obstetric practice for that woman	**2+**	**D**	Choices around mode of birth should follow routine obstetric practice

Women and pregnant people with ICP do not have increased rates of assisted or operative birth compared with women without ICP.[50] Mode of birth should therefore be based on usual obstetric or medical indications. If planned early birth is indicated, induction of labour should be considered unless other reasons for caesarean birth are present. *[Evidence level 2+]*

8.3 | Monitoring in labour

Recommendation	Evidence quality	Strength	Rationale for the recommendation
• **Offer continuous electronic fetal monitoring (CEFM) to women with peak bile acids 100 micromol/L or more.** • **There is insufficient evidence for or against CEFM in women with peak bile acids below 100 micromol/L. A shared decision can be made based on co-morbidities and preferences.** **Advise women that the presence of risk factors (such as gestational diabetes, pre-eclampsia, multifetal pregnancy) appear to increase the risk of adverse perinatal outcomes and that these conditions themselves may necessitate monitoring during birth or in conjunction with ICP may influence decision-making around monitoring in labour.** **Advise women that meconium-stained liquor is more common in moderate and severe ICP, and that this will influence decision-making around CEFM**	4	D	Recommendation based on extrapolation from assessment of fetal risk associated with stillbirth and other adverse perinatal outcomes, highlighted by systematic review

If the woman or pregnant person has existing obstetric or medical conditions that influence decision-making around fetal monitoring in labour, these should be taken into account when planning intrapartum care. In women with mild ICP (peak bile acids 19–39 micromol/L) and no other risk factors, intrapartum care can follow national guidelines.[33] In women with moderate ICP (peak bile acids 40–99 micromol/L), the decision should be made on an individualised basis, explaining that the benefit of continuous electronic fetal monitoring is uncertain; the presence of any other risk factors should be taken into account. In women with severe ICP (peak bile acids 100 micromol/L or more), in light of evidence that there is a risk of adverse perinatal outcomes in these women, continuous electronic fetal monitoring should be offered. Women with moderate and severe ICP are more likely to have meconium-stained liquor, and this will influence the need for continuous electronic monitoring in labour. *[Evidence level 4]*

8.4 | Analgesia in labour

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Offer women with uncomplicated ICP standard analgesia and anaesthesia options for birth	4	D	Choice of analgesia should be based on routine clinical practice

There are no studies that have indicated that women or pregnant people with ICP require different options for analgesia and anaesthesia for birth and national guidance should be followed.[33] Three cohort studies of 223 women,[17] 531 women[15] and 745 women[18] with ICP described above in Section 4.2, who had routine coagulation testing reported no cases of prolonged prothrombin time in women with uncomplicated clinical presentations. The small number of abnormal results occurred in women with alternative diagnoses (such as acute fatty liver of pregnancy). *[Evidence level 4]*

8.5 | Third stage of birth

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Advise women that there is no evidence of an increased risk of postpartum haemorrhage if they have uncomplicated ICP	2–	D	Care of third stage should follow routine clinical practice

A case–control study (64 cases)[50] and case-cohort study (348 cases)[51] both showed no increased risk of postpartum haemorrhage in women with ICP. Standard care using national guidance for the third stage of birth should be followed.[33] *[Evidence level 2–]*

9 | WHAT FOLLOW-UP SHOULD BE OFFERED TO WOMEN WHO HAVE HAD A PREGNANCY AFFECTED BY ICP?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
For women who have uncomplicated ICP, follow-up should be arranged at least 4 weeks after birth to confirm resolution of ICP. Advise them that they should anticipate itching and raised maternal bile acid concentrations to resolve after birth	4	D	Good practice to arrange follow up

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In women who have had ICP, itch usually stops after birth, often in the first few days, and liver function tests and bile acid concentrations should return to normal within a few weeks. At postnatal follow-up, the healthcare professional should ensure that itching has resolved and should confirm that maternal bile acid concentrations and liver function tests have normalised. If itching or biochemical abnormalities persist beyond 6 weeks postpartum, consider other diagnoses depending upon the history and examination findings. Referral to a hepatologist may be required. *[Evidence level 4]*

9.1 | What advice should be offered for future contraceptive or hormonal options?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Advise women that ICP itself does not influence their choice of contraception or hormone replacement therapy	**4**	**D**	Choice of contraception should follow UK Medical Eligibility Criteria (UKMEC) guidance
For women with ICP and previous cholestasis secondary to combined hormonal (oestrogen-containing) contraception, advise them to use progestogen-only or non-hormonal methods	**4**	**D**	This is in line with UKMEC guidance
In women with previous ICP requesting HRT, consider offering if there are no other contraindications to use	**4**	**D**	Extrapolated from UKMEC guidance on exogenous oestrogen use

As with all women and pregnant people, discussion about methods of contraception should begin during the antenatal period[21] and continue in the early postpartum days.[52] This should include the health benefits of spacing pregnancies, consideration of medical conditions and/or patient characteristics affecting contraceptive choice (such as venous thromboemblism risk factors, breastfeeding, medical history), the reliability and benefits of long-acting reversible contraceptive methods, and the additional use of condoms if there is a risk of sexually transmitted infections and HIV.[53] *[Evidence level 4]*

The 2016 UK Medical Eligibility Criteria (UKMEC) for Contraceptive Use advises that copper-bearing intra-uterine devices, levonorgestrel-releasing intra-uterine systems, progestogen-only implant, progestogen-only injectable, and progestogen-only pill can be used without restriction in women with a history of ICP (UKMEC category 1).[53]

Combined hormonal contraception can be used in women with ICP (UKMEC 2) provided they do not also have a history of contraception related cholestasis. It was previously thought that women with a history of ICP may have an increased risk of developing cholestasis when using oestrogen-containing hormonal contraception, but this is unlikely for the majority of women. The 2016 UKMEC states that in women who have had ICP the advantages of using these oestrogen-containing methods outweigh this theoretical risk (UKMEC category 2)[53] and women may thus choose to use this method. Resolution of itching and liver function tests and bile acid concentrations returning to normal levels should be confirmed before commencing this method. *[Evidence level 4]* Advise women to attend for review if recurrence of itch and abnormal liver function tests occur while using combined hormonal contraception, this would give a diagnosis of contraceptive-related cholestasis (UKMEC 3) and alternative contraception options should be discussed. *[Evidence level 4]*

For women with an atypical presentation of ICP, atypical postnatal clinical course, where other diagnoses are suspected, or where itching and liver function tests have not resolved, a personalised approach to contraceptive choice should be undertaken, with provision of information about avoidance of pregnancy with active liver disease.

For menopausal women considering hormonal replacement therapy (HRT), national recommendations should be followed.[54] Current UKMEC guidance is that oestrogen-containing contraception can be used in women with a history of ICP. It therefore seems reasonable to offer the lower physiological dose of oestrogen found in HRT, with review of use if women develop itching or other signs of cholestasis.

9.2 | How should women be cared for in future pregnancies?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Advise women with a history of ICP that they have an increased chance of recurrence of ICP in subsequent pregnancies	**3**	**D**	Good practice to inform women of likelihood of recurrence
Perform a baseline liver function test and bile acid concentration with booking blood investigations	**3**	**D**	Good practice to establish baseline values

Women and people of reproductive age who have had a pregnancy complicated by ICP have an increased chance of ICP in a subsequent pregnancy compared to the general pregnancy

population, but the precise magnitude of this is unclear, as quoted rates of recurrence are based on small studies (e.g. of 18 women[55] and 69 women[56]) and the results may not be generalizable to a wider UK population with ICP. At booking in subsequent pregnancies, baseline measurement of liver function tests and bile acid concentrations should be performed in order to establish that these are normal. They should only be repeated if clinically indicated. *[Evidence level 3]*

10 | RECOMMENDATIONS FOR FUTURE RESEARCH

- In women with ICP:
  - Which maternal or fetal prognostic tools and/or monitoring modalities predict adverse perinatal outcome (including preterm birth and stillbirth)?
  - Should women with ICP be tested for gestational diabetes (and by what method)?
  - What is an effective treatment for itching?
  - What is an effective treatment to prevent adverse perinatal outcomes?
- In pregnant women with raised bile acids, what is the natural history of bile acid concentrations without treatment?
- What is the ongoing risk of adverse pregnancy outcome in women whose bile acid concentrations normalise?
- What is the cause of itching in women without raised bile acids, and what is an effective treatment for their itching?

11 | AUDITABLE TOPICS

- Proportion of women with raised bile acid concentrations offered timing of birth in line with RCOG Green-top Guideline. (>90%)
- Proportion of women with uncomplicated raised bile acid concentrations having additional investigations routinely performed. (<10%)
- Proportion of women with raised bile acid concentrations offered ursodeoxycholic acid in line with RCOG Green-top Guideline. (<5%)
- Proportion of women with severe ICP (peak bile acids ≥100 micromol/L) offered continuous electronic fetal monitoring during labour. (>90%)

These targets have been set in recognition of the need for individualised care particularly in women with comorbidities and atypical ICP.

12 | USEFUL LINKS AND SUPPORT GROUPS

- Information for healthcare professionals
  - Maternal use of medication in pregnancy (UK Teratology Information Service) (http://www.uktis.org/html/maternal_exposure.html)
  - http://www.uktis.org/html/maternal_exposure.html
- Information for women and families
  - Research based charity and support group ICP Support (http://www.icpsupport.org/)
  - RCOG. *Intrahepatic Cholestasis of Pregnancy*. Information for you (https://www.rcog.org.uk/for-the-public/)
- Information for women and their families on use of medicines in pregnancy
  - http://www.medicinesinpregnancy.org/

CONFLICT OF INTERESTS

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.**How to cite this article:** Girling J, Knight CL, Chappell L; on behalf of the Royal College of Obstetricians and Gynaecologists. Intrahepatic cholestasis of pregnancy. BJOG. 2022;129(13):e95–e114. https://doi.org/10.1111/1471-0528.17206

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APPENDIX 1

Explanation of guidelines and evidence levels

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1 *Development of RCOG Green-top Guidelines* (available on the RCOG website at http://www.rcog.org.uk/green-top-development). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of Recommendation

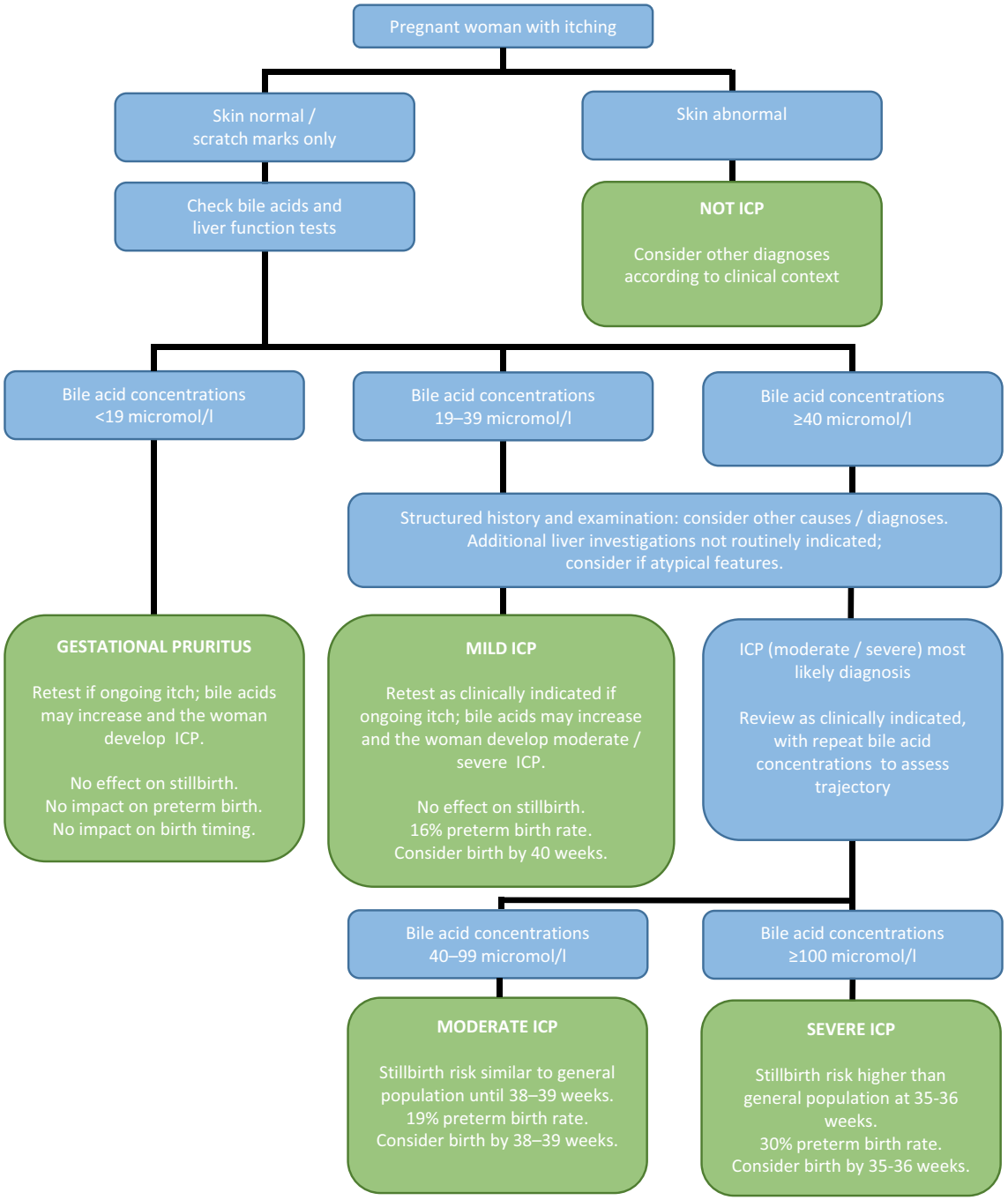
Grade of Recommendation: A	At least one meta-analysis, systematic reviews or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
Grade of Recommendation: B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
Grade of Recommendation: C	A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
Grade of Recommendation: D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good Practice Points

Grade of Recommendation: ✓	Recommended best practice based on the clinical experience of the guideline development group

APPENDIX 2

Flowchart for the care of pregnant women with itching



Figures above relate to singleton pregnancy with no other risk factors.

Comorbidities (particularly pre-eclampsia and diabetes) or other obstetric risk factors (such as multifetal pregnancy), are associated with increased risk of stillbirth and should be taken into consideration when planning management.

Additional liver investigations may be considered in women with atypical features (e.g. early onset, marked transaminitis, jaundice, fever, or in whom postpartum resolution does not occur). These investigations may include liver ultrasound, viral hepatitis screen, liver autoimmune tests, and/or coagulation screen.

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APPENDIX 3

Summary of care for pregnant women with itching and normal skin

	Otherwise uncomplicated low risk singleton pregnancy[a] Itching with normal skin/excoriations Peak total BA concentration, micromol/L			
	<19 micromol/L	**19–39 micromol/L**	**40–99 micromol/L**	**≥100 micromol/L**
Initial diagnosis	Pruritus gravidarum	Mild ICP	Moderate	Severe ICP
	Structured history and examination, no additional or alternative causes identified			
If itch persists, frequency of BA	1–2 weekly	1–2 weekly	1–2 weekly	Only if will impact care plans
Risk of stillbirth compared with general obstetric population [0.18–0.75]	Unchanged	Unchanged 0.13%	Unchanged until 39 weeks, 0.28%	Raised, 3.44%
Timing of mode of birth	No impact	Consider planned birth by 40 weeks	Consider planned birth at 38–39 weeks	Consider planned birth at 35–36 weeks
Preterm birth rate, spontaneous and iatrogenic	Unchanged	16%	19%	30%
Role for routine use of UDCA	No	No	No impact on stillbirth	No impact on stillbirth
Additional liver investigations[b]	Not indicated routinely. Consider for women with atypical features (e.g. early onset, marked tranaminitis, jaundice, fever, or in whom postpartum resolution does not occur)			

[a] For pregnancies with other obstetric or medical conditions, these should be taken into consideration when deciding management options.

[b] Such as liver ultrasound, viral hepatitis screen, liver autoimmune tests. ICP, intrahepatic cholestasis of pregnancy; UDCA, ursodeoxyxholic acid.

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The final version is the responsibility of the Guidelines Committee of the RCOG.

DISCLAIMER

The Royal College of Obstetricians and Gynaecologists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available.
This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.

The guideline will be considered for update 3 years after publication, with an intermediate assessment of the need to update 2 years after publication.