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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