

Intrahepatic Cholestasis of Pregnancy – Diagnosis and Management:

**A Consensus Statement of the Society
of Obstetric Medicine of Australia
and New Zealand (SOMANZ)**

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Abstract

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a liver disease specific to pregnancy, characterised by pruritus and increased total serum bile acids (TSBA), with an Australian incidence of 0.6-0.7%. The pathophysiology involves genetic, hormonal and environmental factors. It is associated with stillbirth and preterm birth, and warrants multidisciplinary involvement, particularly when it is severe (TSBA ≥ 40 $\mu\text{mol/L}$) or very severe (TSBA ≥ 100 $\mu\text{mol/L}$), or with early onset (prior to 36 weeks' gestation). The benefit versus risk of an iatrogenic preterm birth for ICP pregnancies remains uncertain. The evidence base for management is limited. This is the first Australian and New Zealand consensus statement on the diagnosis and management of ICP, released under the auspices of the Society of Obstetric Medicine of Australia and New Zealand.

Main recommendations

ICP can be diagnosed by non-fasting TSBA ≥ 19 $\mu\text{mol/L}$ in the absence of pre-existing liver disorders in a pregnant woman with pruritus without a rash.

Severe and very severe forms of the disease (TSBA concentrations ≥ 40 $\mu\text{mol/L}$ and ≥ 100 $\mu\text{mol/L}$ respectively) identify women at increased risk of spontaneous pre-term birth (severe) and stillbirth (very severe).

Benefit-versus-risk for iatrogenic preterm birth in ICP remains uncertain. Ursodeoxycholic acid (UDCA) remains the best treatment available for women remote from term, its use improving perinatal outcome while also reducing pruritus, although it has not been shown to reduce stillbirth.

Main change to current management practice

Measurement of TSBA should be performed on **non-fasting** samples, as fetal risk is dependent on peak TSBA concentrations, irrespective of fasting.

Methods

The Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) formed a multidisciplinary writing team of those with expertise in ICP, including obstetricians, obstetric physicians, laboratory scientists, a midwife, a clinical pharmacist, a neonatologist and an epidemiologist, from both Australia and New Zealand, to develop a consensus statement designed to provide practical guidance to clinicians faced with caring for women with ICP. The writing group members were drawn from a variety of clinical backgrounds, including practitioners from metropolitan, regional and rural/remote settings. We have completed this expert consensus statement, the data being too limited to apply the full National Health and Medical Research Council standards for guidelines.

The evidence for this review was selected after a search in the English literature encompassing the years 2000-2021. The search terms included 'cholestasis'; 'intrahepatic cholestasis'; 'ursodeoxycholic acid'; 'pruritus'; 'pregnancy complications'; 'newborn disease'; 'prenatal disorder'; 'liver function tests'; 'bile acids'; 'bile salts'. The search was complemented by reference lists and suggestions from writing group members. The literature was also searched for other relevant guidelines and reviews, identifying 4 national¹⁻⁴ and 2 supranational^{5, 6} guidelines for management of ICP.

Following literature review, each member of the writing group contributed to development of the document, which was then reviewed by all authors, with suggestions and iterative changes made. Regular meetings were held, and a consensus of expert opinion was achieved. We have graded the recommendations according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system⁷, highlighting in the text "**Evidence-based recommendations with an assessment of the strength of the evidence**", where there is high-level evidence from systematic reviews and meta-analyses, Conditional recommendations, where the evidence is not as strong, and "*Good practice points*" where evidence is not available, as well as tabulating these (Table 3) (see Table 4 for key).

The statement has been reviewed by the SOMANZ Council, and disseminated to members throughout Australia and New Zealand, together with other professional bodies for stakeholder review. The writing group would like to acknowledge the valuable and extensive feedback provided. Each item of feedback was reviewed by the writing group and a consensus decision was made in response to each item of feedback.

Acknowledgments

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Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a liver disease specific to pregnancy⁸, characterised by pruritus and increased total serum bile acids (TSBA), after excluding other causes of pruritus. The incidence in Australia is 0.6–0.7%^{9, 10}. The abnormalities resolve after pregnancy. It is associated with preterm delivery, possibly related to bile acid-induced increased expression of myometrial oxytocin receptors¹¹. The most feared, but rare, complication of ICP is intrauterine fetal demise, especially after 37 weeks' gestation. This may be related to a toxic effect of bile acids on fetal cardiomyocytes¹², but placental dysfunction or placental vessel spasm have also been proposed as possible mechanisms.

Epidemiology

Significant ICP disparities exist. Araucanian Indians in Chile have an ICP prevalence 10-fold higher than other population groups¹³. A population study in Sweden reported an incidence of 1.5%¹⁴. A UK Indian subcontinent population showed a twofold increase in ICP prevalence compared with Caucasians¹⁵.

Family history of ICP affects the incidence. In a Finnish study (N=11,984, ICP-n=65), >30% had affected siblings, equating to an increased risk from 0.54% in the general obstetric population to 6% for siblings of a primary case (Odds Ratio 12.6[95% Confidence Interval (CI) 5.6–28.1])¹⁶.

ICP is five times more frequent in women with a multiple gestation¹⁷, is more common in women with positive hepatitis C serology¹⁸ and occurs at an earlier gestation in such women¹⁹, although the reasons for these observations are not understood. Cholelithiasis, past or present, is also more common in women with ICP²⁰. A recent report has drawn attention to an ICP-like syndrome associated with previous azathioprine therapy for inflammatory bowel disease in pregnancy, resolving after withdrawal of the drug²¹.

Several genetic variants of bile acid (BA) transporters, which underlie various forms of neonatal and infant cholestasis, have been reported in women who have experienced ICP. These include Phosphatidylcholine floppase multidrug resistance protein 3 (MDR3: *ABCB4*), Bile salt export pump (BSEP: *ABCB11*), Phosphatidyl serine flippase (*ATP8B1*), Multidrug resistance-associated protein 2 (MRP2: *ABCC2*), Tight junction protein 2 (*TJP2*), and Farnesoid X receptor (*FXR*)²². Further large-scale analyses of whole-genome sequencing in women with a history of severe early onset ICP have recently identified common sequence variation in liver-enriched genes and liver-specific *cis*-regulatory elements as contributing mechanisms to ICP susceptibility²³.

Clinical Features

The main maternal symptom is a cholestatic pruritus, which ranges from mild to very severe, affecting sleep and mental state²⁴. The typical initial distribution is to palms and soles, though it can progress and become generalised²⁵. There is no associated rash; however, excoriations are common. The urine may become dark because of excreted bile pigments. Jaundice and steatorrhea are rare complications. It most often presents in the third trimester, but 5% of cases have been reported in the first trimester²⁶.

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Pathology

The cholestasis is intrahepatic, with normal hepatic architecture apart from some bile accumulation with plugging and thrombi²⁷.

Biomarkers:

The relationship of TSBA to the onset of pruritus in pregnancy has been a long standing conundrum²⁸. *If pruritus in pregnancy persists with normal TSBA concentrations and/or serum transaminases, then repeat testing is indicated every 1–2 weeks, to establish or refute the diagnosis of ICP²⁹.*

CONDITIONAL

Diagnosis

The diagnosis is one of exclusion, supported by increased concentrations of non-fasting TSBA in the presence of pruritus without other active hepatic pathology, which can often contribute to their increase, or concomitant dermatosis, which may confound diagnosis. TSBA are a hallmark of ICP, and easy access to timely assays is needed. Alanine transaminase (ALT) measurements are not required for diagnosis, and are not good markers of itch or of pregnancy outcome; increased TSBA concentrations may suggest consideration of other diagnoses. [See Table 1] A careful medical, obstetric and social history, together with a full examination, are required.

Large-scale multinational clinical trials, relying on diagnoses derived from biochemical results, may overlook the importance of assay standardisation. TSBA measurements use varying standards, which needs to be addressed³⁰.

Differential diagnoses (See Table 1)

Drug-induced liver injury should be considered. History should exclude chronic paracetamol intake, alcohol abuse, antibiotics (e.g., penicillins, clavulanic acid, cephalosporins, erythromycin and nitrofurantoin), recent halothane anaesthesia (perhaps administered overseas and not well documented in medical reports), labetalol and methyldopa, together with non-prescribed and herbal medications, and ingestion of various fungi (psychedelic and culinary).

A history of childhood jaundice with pruritus (non-infective and post-neonatal) and oral contraceptive-related pruritus and/or jaundice warrant consideration of genetic causes of cholestasis, including benign recurrent intrahepatic cholestasis (BRIC) and progressive familial intrahepatic cholestasis (PFIC).

Pre-existing liver disease, e.g., primary biliary cholangitis, sclerosing cholangitis and autoimmune hepatitis, excludes the diagnosis of ICP by definition, although worsening cholestasis may be seen during pregnancy with these conditions. *Autoimmune liver disease rarely presents in pregnancy. If there is a family history of autoimmune disorders (e.g., thyroid, rheumatoid, type 1 diabetes mellitus), and TSBA ≥ 40 $\mu\text{mol/L}$ or transaminases exceed 200 U/L (5x Upper Limit of Normal) or presentation is prior to 34 weeks, an autoimmune screen is warranted.* [see Table 2]

Chronic hepatitis C increases the risk of ICP²⁰. Booking serology should be checked and retested if needed. An acute viral hepatitis screen can be considered if there is clinical suspicion. [see Table 2]

Pregnancy-specific disorders can coexist with ICP. Anorexia, malaise and vomiting are suggestive of other disorders, e.g., acute fatty liver of pregnancy (AFLP), which can occur in conjunction with ICP³¹. *A recent Australian population study reported a threefold increase in the risk of gestational diabetes (GDM) with ICP and a 10-fold increase in the risk of pre-eclampsia with ICP⁹. Dermatoses of pregnancy rarely co-exist with ICP³².*

The risk of pre-term birth and of stillbirth is dependent on the peak titre of TSBA³³: there are as yet no reliable data to suggest that a fall in serum BA from a peak value can be construed as a definite risk reduction, even though experienced clinicians might be willing to consider the possibility of such in the clinical management of a woman with severe ICP, who has presented remote from term. **Spontaneous preterm labour is increased in frequency and there is an increased incidence of meconium-stained liquor and fetal asphyxial events in women with TSBA ≥ 40 $\mu\text{mol/L}$ ¹⁴. The risk of stillbirth overall is small but increased (Hazard ratio (HR) 30.50 [95% CI 8.83–105.30]; $p < 0.0001$) in women with TSBA ≥ 100 $\mu\text{mol/L}$ ³³.**

*A non-fasting TSBA ≥ 19 $\mu\text{mol/L}$ can be used as a reliable threshold for diagnosis of ICP, with good sensitivity and specificity³⁴.**

Severe ICP should be diagnosed in women with peak TSBA ≥ 40 $\mu\text{mol/L}$, given the association with increased spontaneous preterm birth beyond 34 weeks, meconium-stained liquor and fetal membranes, and fetal asphyxial events¹⁴.

Very severe ICP should be diagnosed in women with peak TSBA ≥ 100 $\mu\text{mol/L}$ given the association with an increased risk of stillbirth³³. [Figure 1]

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*. If a fasting sample is used, TSBA values ≥ 10 $\mu\text{mol/L}$ are an alternative to identifying mild disease: the specificity of ICP diagnosis is higher with fasting samples, but the sensitivity is very low ($< 30\%$) for mild disease.[32]

Therapeutic options

Depending on the severity and the gestation at presentation, pharmacological options may not always be required, particularly given the relative uncertainty of benefit for the various proposed treatments, as discussed in the most recent Cochrane review and systematic reviews/meta-analyses³⁵. The risks of spontaneous preterm birth must be carefully weighed against those of preterm intervention, both increased in severe disease.

Most women with ICP, especially those with mild disease, show a progressive fall in TSBA as pregnancy progresses, even without treatment³⁶.

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Ursodeoxycholic acid (UDCA) can be recommended for treatment in women remote from term. It has been shown to improve biliary flow³⁷, enhance the protective bicarbonate environment on the surface of cholangiocytes³⁸, and reduce bile acid-induced apoptosis³⁹. When administered, UDCA replaces the more toxic hydrophobic BAs (such as cholic acid) in the circulating BA pool⁴⁰. UDCA has also been shown *in vitro* to protect rat cardiomyocytes from damage by endogenous bile salts⁴¹. *Oral UDCA, compared with placebo, results in a small improvement in pruritus score as measured on a 100 mm visual analogue scale (VAS) (mean difference (MD) -7.64 points [95% CI -9.69 to -5.60 points; 2 trials, 715 women]³⁵.*

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In the PITCHES trial (a randomised controlled trial (RCT) comparing UDCA with placebo), most women with ICP, especially those with mild disease, showed a progressive fall in TSBA as pregnancy progressed, even without treatment³⁶. While the 25% reduction of itch was not thought to be helpful by women or professionals in the PITCHES trial³⁶, clinical experience suggests that some relief of itch is better than none, which might lead to demands for premature birth, given the intensity of some women's pruritus. The reduction in TSBA was less in the UDCA arm of PITCHES, likely reflecting the measurement of orally administered UDCA within the total measured TSBA concentration⁴⁰. There was, however, a significantly greater reduction of ALT concentrations and pruritus score in the UDCA arm for the remainder of the pregnancy³⁶.

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A recent systematic review and individual participant data (IPD) meta-analysis, (85 studies, in 6974 women with ICP, of which 34 studies contributed data to the meta-analysis) reported that UDCA treatment had no effect on the prevalence of the composite outcome of stillbirth and preterm birth (adjusted Odds Ratio[aOR] 1.28, 95% CI 0.86-1.91; p=0.22). However, when the analysis was limited to the only four available RCTs, there was a reduced incidence of the composite outcome (aOR 0.60, 0.39-0.91; p=0.016), and of spontaneous preterm birth (<37 weeks' gestation) in singleton pregnancies⁴²: although the 25% reduction in aOR for spontaneous preterm birth in singleton pregnancy before 34 weeks' gestation was not significant (95% CI 0.23-1.22; p=0.65), the event rate was low at this gestation (5/387 cf 6/366), and the study may be underpowered to show a difference. We do not recommend tocolysis for this group. The event rate for stillbirth alone in these studies is very low (1/439, cf 3/429). To date, there is no adequately powered study to assess effect on stillbirth rate⁴².

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The oral UDCA dosage is based on severity, with an initial dose of 500mg daily in mild cases, or 1500mg daily in severe cases, using twice-daily dosing regimens, increasing weekly to a maximum 2000 mg daily (20 mg/kg).

Availability and cost of UDCA may differ by country and region. In New Zealand, practitioners can apply for a subsidy by special authority for treatment of ICP. In Australia, UDCA is not listed on the Pharmaceutical Benefits Scheme for treatment of ICP, but most public hospitals will provide subsidised access for eligible patients. Alternatively, a private prescription for UDCA can be taken to any community pharmacy for dispensing (noting the considerable out-of-pocket cost associated with this approach).

Other treatment options

Rifampicin, a semisynthetic antibiotic and a first-line agent for treatment of tuberculosis, including in pregnancy^{43, 44}, has been shown to reduce serum BA in the management of cholestasis in non-pregnant populations. It is a pregnane X-receptor (PXR) agonist and a potent inducer of key enzymes in the hepatic and intestinal detoxification machinery (such as *CYP3A4*, *CYP2D*, *UGT1A1*, *SULT2A1*) and export pump *MRP2*⁴⁵. Systematic review has shown that, in patients with cholestatic pruritus, rifampicin, compared with placebo, showed benefit with a low incidence of adverse events⁴⁶. Rifampicin has been used anecdotally in ICP⁴⁷, and is currently being investigated in an ongoing randomised controlled trial, the TURRIFIC trial (ANZCTR 374510), comparing it with UDCA in the reduction of pruritus in ICP⁴⁸.

Other treatment options³⁵ include the anion-exchange resin cholestyramine, the mu-opioid antagonists naltrexone and naloxone, and the serotonin reuptake inhibitor sertraline. These drugs are recommended by evidence-based guidelines in non-pregnant patients in a stepwise therapeutic approach⁶. However, such drugs should only be used in ICP under the supervision of experienced clinicians. *If drugs such as cholestyramine, which inhibit dietary vitamin K uptake, are used, maternal coagulation needs to be monitored, so that parenteral vitamin K can be provided if necessary⁴⁹.*

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There is **currently insufficient evidence** from randomised trials to indicate that s-adenosyl methionine (SAME), guar gum, activated charcoal, dexamethasone, cholestyramine, traditional remedies, or novel therapies (e.g., inhibitors of the apical bile acid transporter) are effective in treating women with ICP³⁵.

Antihistamines, including non-sedating cetirizine 10 mg one to two times a day and/or sedating promethazine 25 mg at night, may provide relief from pruritus; however, these are untested in RCTs. Sedating antihistamines may also aid sleep.

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Non-pharmacological management

There are no trials of the efficacy of topical emollients, although these are likely to be safe and may be useful treatment adjuncts. Women should be advised to avoid hot showers and scratching or rubbing the skin. Plain sorbolene moisturising cream/lotion, liquid paraffin, pine tar solution, aqueous cream with menthol, or bicarbonate of soda baths may provide symptomatic relief.

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Ultraviolet phototherapy has been used in pregnancy for other dermatoses⁵⁰, but there are no data available for its use in ICP. *If used, care should be taken to provide folic acid supplements as there is a risk of depletion⁵¹.*

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Pruritus is a profoundly distressing symptom. Compassionate therapeutic relationships, high-quality nutrition, adequate sleep, hydration, keeping cool, use of cool compresses, cool (i.e., kept in the fridge) topical emollients, gentle movement, sunshine exposure, social contact, going into nature, engaging activities and audio-visual distraction are all important considerations.

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Management

Clinicians may discuss (pre-conceptually or antenatally) with high-risk women (e.g., with previous ICP) the importance of reporting pruritus. However, it is uncertain whether this changes management or improves outcomes.

Antenatal

Multidisciplinary management is essential for ICP, including midwives, GPs, obstetricians and obstetric physicians. *Urgent referral and consult/transfer of care should be arranged in severe/very severe cases (TSBA $\geq 40/\geq 100$ $\mu\text{mol/L}$), with continuing ongoing maternity care at a referral centre, especially for early onset (before 36 weeks') cases.*

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Once a diagnosis of ICP is established, regular assessment and review of TSBA should be initiated, fortnightly in the third trimester for mild ICP (TSBA 19-39 $\mu\text{mol/L}$), or weekly in severe cases (TSBA ≥ 40 $\mu\text{mol/L}$) [see Fig. 1]. A rapid rise in TSBA at this gestation might impact on decisions about early birth. Once TSBA reach ≥ 100 $\mu\text{mol/L}$, there is no value in further testing to identify additional risk. Given that TSBA assays are not well standardised^{30, 52}, serial monitoring should ideally be performed using the same laboratory. If treatment with UDCA is commenced, blood should be drawn for TSBA assay shortly before the next dose is taken, as UDCA is a BA, and may contribute up to 60% in the assay⁴⁰, although a fasting sample is not required.

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Coagulation studies, checking for prothrombin time/international normalised ratio (PT/INR) and/or activated partial thromboplastin time (APTT), should be performed after a diagnosis of severe/very severe ICP (serum TSBA $\geq 40/\geq 100$ $\mu\text{mol/L}$). Coagulation tests should be repeated prior to elective birth. If there is an increased INR (≥ 1.4) or APTT (≥ 40 seconds), treatment with parenteral vitamin K 10 mg IV should be initiated, and further assessment performed weekly. Oral vitamin K may not be effective in cholestasis, due to poor gastro-intestinal absorption.

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Birth plans

Plans for birth should be made in consultation with the woman, including discussion of the risks and benefits of planned birth before <39 weeks', if:

- severe ICP (peak serum TSBA $\geq 40 \mu\text{mol/L}$) $\geq 38^{+0}$ weeks'
- very severe ICP (peak serum TSBA $\geq 100 \mu\text{mol/L}$) at or after 36⁺⁰ weeks'

(Some authorities recommend even earlier birth for women with very severe ICP (e.g., 35-36 weeks')⁴, although the evidence base for this is not strong.)

The risk of stillbirth for TSBA 40-99 $\mu\text{mol/L}$ is 0.28% (comparable to background rates). This risk of stillbirth increases to 3.4% when TSBA exceeds 100 $\mu\text{mol/L}$, most notably from 35 to 36 weeks'³³.

Antenatal admission

Outpatient management is recommended if TSBA <40 $\mu\text{mol/L}$ and the woman remains clinically well.

Admission for assessment and plans for the birth may be considered if TSBA are $\geq 100 \mu\text{mol/L}$, especially after 36 completed weeks of gestation. For those in rural and regional areas, consultation with a referral centre will inform plans. Further outpatient management may be considered if treatment reduces the TSBA to <40 $\mu\text{mol/L}$.

While such data provide helpful guides to management, there are currently no good quality data supporting risk reduction of adverse fetal events in women with ICP, whose TSBA values fall in response to treatment³⁶. Further research is required to determine if timing of birth may be modified by the response to treatment.

Fetal surveillance

In the absence of other maternal or fetal pregnancy complications (e.g., pre-eclampsia, GDM, fetal growth restriction, multi-fetal pregnancy), regular growth ultrasounds and cardiotocography (CTG) monitoring are not required. Case studies have reported intrauterine fetal deaths (IUFD) following a normal CTG (within 7 hours to 5 days) in the presence of documented normal fetal activity prior to the diagnosis of IUFD associated with ICP^{53, 54}.

Umbilical artery Doppler flow measurements have not demonstrated any significant change, nor prediction of adverse fetal risk, in pregnancies complicated by ICP⁵⁵.

Any decrease/absence of fetal movements should be reported urgently and is an indication for fetal assessment and CTG.

Anxiety may be a significant feature in affected women, particularly in those who have had a previous adverse pregnancy outcome. Acknowledgement of the anxiety and empathetic psycho-social support are important components in clinical management.

Intrapartum management

Continuous electronic fetal monitoring in labour is recommended in women with severe/very severe ICP (TSBA $\geq 40/\geq 100 \mu\text{mol/L}$) and should be offered. (Most women with severe ICP do not go into term spontaneous labour and are usually birthed electively. Thus, they are offered EFM intrapartum for reasons other than ICP.)

Coagulation should be checked in women with severe/very severe ICP (TSBA $\geq 40/\geq 100 \mu\text{mol/L}$), and parenteral vitamin K (10 mg IV) should be administered if PT/INR or APTT are abnormal.

Active management of the third stage of labour is recommended, given the increased risk of postpartum haemorrhage (PPH) seen in some early studies^{57, 56}. Although later studies have not confirmed an increased incidence of PPH in ICP⁵⁷, recent small studies have demonstrated hypovitaminosis K, likely secondary to malabsorption of vitamin K, in ICP women, which may help to explain the discrepancy⁵⁸.

Parenteral Vitamin K should be administered to all neonates of women with ICP, especially if their mothers were treated with rifampicin or cholestyramine⁵⁹.

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Postpartum management

Maternal: Pruritus will usually resolve 1-2 days postpartum. *Pharmacological treatment can be ceased at birth.* Any associated maternal jaundice usually resolves in the first postnatal week.

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TSBA concentrations commonly normalise within the first week but should be checked, along with serum transaminases, at 6 weeks postpartum. *Should biochemical abnormalities persist beyond 6 weeks postnatally, further investigations should be performed to exclude underlying liver disease.*

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Hormonal contraception is not contraindicated in women who have experienced ICP but, if pruritus recurs in women using hormonal contraception, further investigation should be undertaken. Consideration should be given to using non-hormonal methods of contraception if liver function remains abnormal.

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For a more in depth discussion of contraception in women with ICP, the reader is directed to the recent RCOG Guideline⁴.

Neonatal: normal routine care and monitoring are required for these infants.

Counselling

Fetal Outcomes:

While the hazards of preterm birth and of stillbirth are dependent on the peak titre of TSBA, once delivered, the baby is removed from the toxic maternal environment, and good outcomes can be expected.

Long term outcomes:

Few studies have investigated the long-term outcome for children of pregnancies complicated by ICP.

A recent study of 6-month-old infants (n=540) from a birth cohort (2018-2020) in Southwest China (n=27058) identified an increased incidence of infantile food allergy in 27/188 (14.4%) children of mothers identified with severe ICP compared with 39/430 (9.1%) children of mothers with no or only mild ICP (χ^2 : p=0.04)⁶⁰. Over 90% of the women were delivered by Caesarean section (mostly electively), and no data were provided as to peripartum antibiotic administration.

In a study (n=45) of 16-year-olds (27 male and 18 female) born to mothers who experienced ICP, who had no other known metabolic disorder (including diabetes and pre-eclampsia) and with a similar maternal Body Mass Index (BMI) in pregnancy, birthweights, placental weights, and gestational ages at birth, males had increased BMI and fasting insulin compared with children from uncomplicated pregnancies. Females had increased waist and hip girth, as well as decreased fasting high-density lipoprotein (HDL) cholesterol relative to females from uncomplicated pregnancies⁶¹. Further studies are needed to explore the potential impact of treatment on such children following maternal treatment during pregnancy.

Females, whose mothers have experienced ICP, are at increased risk of developing this condition during their own pregnancies.

Long term maternal outcomes:

The risk of recurrence of ICP in a subsequent pregnancy is reported to range from 40%⁹ to 70%⁶² and female family members have an increased risk of ICP.

Women, who have had severe ICP, are at risk of chronic liver disease and should have long-term follow-up.

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These risks have been explored in large Swedish population registry studies. While pruritus usually resolves quickly postpartum, affected women have an increased risk of hepatobiliary disease in later life, including liver and biliary tree cancer (HR 3.61, 95% CI 1.68-7.77, and 2.62, 95% CI 1.26-5.46, respectively)⁶³. In the same study, ICP was also associated with later immune-mediated diseases (HR 1.28, 95% CI 1.19-1.38), specifically diabetes mellitus (HR 1.47, 95% CI 1.26-1.72), thyroid disease (HR 1.30, 95% CI 1.14-1.47), psoriasis (HR 1.27, 95% CI 1.07-1.51), inflammatory polyarthropathies (HR 1.32, 95% CI 1.11-1.58) and Crohn's disease (HR 1.55, 95% CI 1.14-2.10).

ICP is a metabolic stress test for the liver, so GPs need to be aware of the long-term risks, even though there is as yet no consensus on what follow-up is appropriate. *An annual check of liver biochemistry seems prudent.*

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Research topics

New diagnostic approaches have included measurement of the lysophospholipase, autotaxin (ATX), as a potential mediator of cholestatic pruritus. Serum ATX is a specific marker for pruritus of cholestasis, but not pruritus of uraemia, Hodgkin's disease, or atopic dermatitis⁶⁴. Whereas BA sequestrants, which reduce BA concentrations, may not impact either pruritus or serum ATX, these can both be modulated in the non-pregnant cholestatic patient by rifampicin and by treatments, such as molecular adsorbent recirculation systems (MARS) or nasobiliary drainage⁶⁴. Serum autotaxin has shown excellent sensitivity and specificity in distinguishing ICP from other pruritic disorders or pre-eclampsia/HELLP-syndrome, and it correlates with the rise in pruritic symptoms⁶⁵.

Other metabolites of interest include progesterone sulfate compounds, which have been identified as increased in women at 9-15 weeks of gestation and prior to symptom onset, and therefore predictive of subsequent ICP. Concentrations of progesterone sulfates were associated with itch severity and, in combination with autotaxin, distinguished pregnant women with itch who would subsequently develop ICP rather than pruritus gravidarum, and were increased in serum from low-risk asymptomatic women who subsequently developed ICP⁶⁶. Such metabolite assays are not routinely available, as they currently require gas chromatography–mass spectrometry and electrospray–mass spectrometry, and to date are not appropriate for clinical management.

Dysregulated BA synthesis might be a key pathogenic finding in ICP: BAs are synthesized from cholesterol via cholesterol 7 α -hydroxylase (*CYP7A1*) and excreted with bile into the duodenum. In the distal ileum, ~99% of BAs are actively taken up by the ileal bile acid transporter (IBAT/ASBT) and transported back to the liver via the portal vein (enterohepatic circulation). In the terminal ileal enterocytes, BAs bind to the nuclear receptor farnesoid X receptor (FXR), which induces the excretion of fibroblast growth factor 19 (FGF19) that, in a negative feedback loop, reduces hepatic BA synthesis by downregulating *CYP7A1*. In severe cholestasis, FXR may also regulate BA synthesis in the liver via small heterodimer partner. FXR also regulates hepatic BA uptake via sodium (Na⁺)-taurocholate co-transporting polypeptide (NTCP) and hepatic BA excretion via the BSEP. Given that 1) gestational hormones (in particular, progesterone sulfates) interfere with the BA uptake at NTCP, resulting in impaired FXR signalling⁶⁷, and 2) BA synthesis can reliably be estimated by measuring the BA precursor 7 α -hydroxy-cholestene-4-one (C4)⁶⁸, it may be that women with ICP differ from unaffected pregnant women in the FXR-dependent regulation of BA synthesis and that UDCA-non-responders are unable to downregulate BA synthesis. Both conditions would be reflected by normal, or even increased, C4 concentrations, despite increased circulating BA. It is unclear when the change in C4 occurs in the pathogenic process or if it is in fact present early in, or even before, pregnancy.

The maternal gut microbiota change significantly throughout pregnancy. BAs, major markers of cholestasis, have complex interactions with the gut microbiota, and there is a dynamic equilibrium between diet-gut microbiome-BA pool size/composition⁶⁹. In addition, recent evidence has shown that the maternal gut microbiota play an important, but ill-defined, role in the aetiology of ICP. Cholestasis in pregnant mice is associated with alterations in the gut microbiota⁷⁰, and the gut microbiota in ICP women are different from those in unaffected pregnancy⁷¹. In addition, the gut microbiota provide an important contribution to the maintenance of normal carbohydrate tolerance and, in the largest population study to date examining the relationship between ICP and GDM, a 2.8 odds ratio (95% CI 2.32–3.41) for GDM was identified in Swedish women with ICP⁷², while in an Australian population, there was a 3.5 increase in the odds ratio (95% CI 2.22 to 5.60) for GDM in women with severe ICP⁹.

Information for Women

ICP Support is a group based in the United Kingdom with an up-to-date website (<https://www.icpsupport.org/>) that provides the following:

- Information about ICP and its impact based on research
- List of published research on ICP
- Information for health professionals
- Support for women via: Facebook pages and groups | Online meetings via Zoom | Worldwide email support

Figure 1: Flow Chart for Diagnosis and Management of Intrahepatic Cholestasis of Pregnancy (ICP)



KEY

TSBA = total serum bile acids | **ALT** = alanine transferase

UDCA = ursodeoxycholic acid | **INR** = International Normalised Ratio | **APTT** = Activated Partial Thromboplastin Time

Table 1: Differential Diagnoses of ICP and Their Clinical Features

Differential Diagnosis	Typical presentation	Features differing from ICP
Pregnancy-Specific cause of itch not pre-existing (which do not exclude the diagnosis of ICP)		
Atopy in pregnancy	Usually first trimester, but can be any gestation	Dry skin, eczematous rash, typical distribution in trunk and limb flexures May have pre-existing history of atopy
Polymorphic eruption of pregnancy	Itchy rash usually second and third trimester, typically around the umbilicus	Papules and plaques, often target lesions. usually affecting lower abdomen with umbilical sparing Normal serum transaminases
Pruritic folliculitis of pregnancy	Usually third trimester	Acneiform eruption, shoulders, upper back, thighs and arms, follicular in nature, maybe pus-filled. Rash improves with advancing gestation
Pemphigoid gestationis	Usually third trimester	Rare, blisters developing, not responsive to ICP therapy
Allergic/drug eruption	Pruritus and rash, any gestation	Maculopapular rash, history of drug or allergen exposure May have abnormal transaminases or increased serum creatinine
Other systemic disease	Pruritus and rash, any gestation	Signs and symptoms of systemic disease History of pre-existing disorder.
Pregnancy-Related liver disorders (which do not exclude the diagnosis of ICP)		
Hyperemesis gravidarum	Nausea and vomiting, First trimester, worse in multiple gestation. Often following assisted reproduction	No itch or rash. Mild to moderate increase in serum transaminases
Acute fatty liver of pregnancy (AFLP)	Nausea, vomiting, jaundice, headache, abdominal pain, usually third trimester	Acute malaise, frequently with acute thirst and polyuria (transient diabetes insipidus), associated with renal and hepatic impairment, coagulopathy, hypoglycaemia, pancreatitis
Haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome	Hypertension, proteinuria, headache, epigastric pain, second or third trimester	Hypertension, proteinuria, not typically associated with itch or rash

Table 1: Differential Diagnoses of ICP and Their Clinical Features (continued)

Differential Diagnosis	Typical presentation	Features differing from ICP
Liver disorders independent of pregnancy (excluding the diagnosis of ICP)		
Viral Hepatitis	May be acute or chronic	Typical viral serology
Autoimmune Hepatitis (AIH)	Less likely to have rash, may have itch, associated with family or personal history of autoimmune disease	Positive autoimmune serology: Antinuclear antibodies (ANA), Smooth Muscle and/or Liver-Kidney Microsomal (LKM) antibodies, and/or positive liver immunoblot
Primary biliary cholangitis (PBC)	Fatigue, pruritus	Positive antimitochondrial antibodies (AMA)
Primary sclerosing cholangitis (PSC)	May be asymptomatic, but pruritus common, often associated with inflammatory bowel disease, especially ulcerative colitis. May overlap with AIH	Non-specific autoantibodies and abnormal immunoglobulins. Typical bile duct "beading" on Magnetic Resonance Cholangio-Pancreatography
Drug-induced liver injury (DILI)	Nausea, vomiting, jaundice, abdominal pain, diarrhoea	Signs and symptoms of systemic disease History of pre-existing disorder.
Biliary obstruction	Nausea, vomiting and abdominal pain	Liver ultrasound usually demonstrates signs consistent with biliary obstruction
Veno-occlusive disease	Jaundice and fluid retention	Usually a complication of chemotherapy

Table 2: Investigations in Suspected or Diagnosed Intrahepatic Cholestasis of Pregnancy (ICP)

Test	Rationale, interpretation
Serum biochemistry	<p>A rise in serum transaminases (ALT, AST) using pregnancy-specific ranges is commonly seen in ICP but is not diagnostic.</p> <p>Other biochemical disturbances may include abnormalities in gamma-glutamyl-transferase (gGT) (uncommon, and may reflect a specific subset of women), and bilirubin (rare). Pregnancy-specific reference intervals must be applied to results where appropriate.</p>
Glucose tolerance testing	<p>A 75g oral glucose tolerance test (OGTT) should be performed as standard. There is an increased incidence of gestational diabetes mellitus (GDM) in ICP.</p> <p>Consideration should be given to a reassessment of glucose tolerance following a diagnosis of ICP, especially if fetal macrosomia is suspected, or ICP is occurring sufficiently preterm for glucose control to be of benefit, using standard reference ranges.</p>
Urinalysis	<p>Check for protein [spot urine protein/creatinine ratio] each visit. There is an increased risk of pre-eclampsia in ICP.</p>
Coagulation studies	<p>Prothrombin time (INR) and activated partial thromboplastin time (APTT) may be prolonged in severe cases, associated with malabsorption of vitamin K. This is particularly important in women who develop steatorrhea.</p>
Upper abdominal ultrasound	<p>Exclude obstructive biliary disease in women with abdominal pain or fever. Gallstones (often asymptomatic) and biliary sludge are also seen more commonly in women with ICP, and may merit surgical review postpartum if present.</p>
Fetal ultrasound	<p>Monitor fetal growth/wellbeing with ultrasound if there are other complications, in particular GDM and pre-eclampsia</p>
Liver biopsy	<p>NOT required, unless other significant pathology is suspected and management would be altered by the biopsy results.</p>
Viral serology	<p>Hepatitis A, Hepatitis B, Hepatitis C, Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) can be tested if there is clinical suspicion, including repeat testing if earlier antenatal screening tests have been performed</p>
Autoimmune serology	<p>Anti-smooth muscle, anti-LKM (liver, kidney microsomal) antibodies and antinuclear antibodies (ANA) (chronic hepatitis), anti-mitochondrial antibodies (primary biliary cholangitis) can be performed in early onset (<30 weeks') or atypical ICP. In otherwise typical ICP, reserve such testing for those women in whom TSBA testing at/after 6 weeks postpartum does not resolve.</p> <p>An autoimmune liver blot may also be useful (good sensitivity).</p>

Table 3: Evidence-based recommendations (in bold), Conditional recommendations (in normal type) and Good practice points (*in italics*)

		GRADE: Certainty & Recommendation
DIAGNOSIS AND CLASSIFICATION of Intrahepatic Cholestasis of Pregnancy (ICP)	<i>The main maternal symptom is pruritus, ranging from mild to very severe, affecting sleep and mental state. The typical initial distribution is to palms and soles but can progress and become generalised. There is no rash but excoriations are common.</i>	
	Base diagnosis of ICP on a <u>non-fasting</u> total serum bile acid (TSBA) concentration $\geq 19 \mu\text{mol/L}$ in the absence of pre-existing liver disorders in a pregnant woman with pruritus without a rash ³⁴ .	LOW: CONDITIONAL RECOMMENDATION
	Identify severe ICP in women with a non-fasting peak TSBA $\geq 40 \mu\text{mol/L}$¹⁴	MEDIUM: RECOMMENDATION
	Identify very severe ICP in women with a non-fasting peak TSBA $\geq 100 \mu\text{mol/L}$³³	MEDIUM: RECOMMENDATION
	<i>ALT measurements are unnecessary for diagnosis and are poor markers of itch and pregnancy outcome. Increased TSBA should suggest consideration of other diagnoses, with other liver abnormalities. (Table 1) A careful previous medical, obstetric and social history needs to be taken, including any pre-existing liver disease, alcohol and/or drug use.</i>	
	In pregnant women with ongoing pruritus without rash, but normal TSBA, repeat testing is indicated every 1-2 weeks, to establish or refute the diagnosis of ICP ²⁹ .	VERY LOW: CONDITIONAL RECOMMENDATION
	<i>In women where a diagnosis of ICP is being considered prior to 30 weeks gestation, or in severe/very severe ICP (peak TSBA $\geq 40/\geq 100 \mu\text{mol/L}$) or where transaminases exceed 200 U/L (5x Upper Limit of Normal), an auto-immune screen should also be conducted (see Table 2).</i>	

Table 3: Evidence-based recommendations (**in bold**), Conditional recommendations (in normal type) and Good practice points (*in italics*) (Continued)

		GRADE: Certainty & Recommendation
DIAGNOSIS AND CLASSIFICATION of Intrahepatic Cholestasis of Pregnancy (ICP) (CONTINUED)	<i>If there is clinical suspicion, women, in whom a diagnosis of ICP is being considered, should have viral hepatitis serology checked or repeated.</i>	
	<i>Women with severe/very severe ICP (peak TSBA $\geq 40/\geq 100$ $\mu\text{mol/L}$) should be warned of the increased risk of spontaneous preterm labour.</i>	
MANAGEMENT MATERNAL ANTENATAL	Pharmacotherapy may not be required, especially after 36 weeks' Use Ursodeoxycholic acid (UDCA) in women who are not close to term to improve perinatal outcomes (composite of stillbirth and preterm birth) and also to reduce pruritus⁴².	MEDIUM: RECOMMENDATION
	<i>Topical emollients are likely to be safe and may be useful adjuncts in treatment.</i>	
	<i>Antihistamines are untested in clinical trials, but may provide some relief of pruritus, and/or aid sleep.</i>	
	Ongoing measurement of TSBA should be performed, at least monthly up to 30 weeks' gestation, every 2 weeks in mild ICP in the third trimester, and weekly in severe/very severe ICP (TSBA $\geq 40/\geq 100$ $\mu\text{mol/L}$), using non-fasting samples, drawn shortly before the next dose of UDCA (if being used) ³⁴ .	LOW: CONDITIONAL RECOMMENDATION
	<i>Multidisciplinary involvement is essential. GPs, obstetricians and midwives should refer and share care for women in mild cases. If the condition presents early (before 36 weeks' gestation) or becomes severe/very severe (TSBA $\geq 40/\geq 100$ $\mu\text{mol/L}$), referral to an experienced clinician is beneficial.</i>	

Table 3: Evidence-based recommendations (in bold), Conditional recommendations (in normal type) and Good practice points (in italics) (Continued)

		GRADE: Certainty & Recommendation
MANAGEMENT MATERNAL ANTENATAL (CONTINUED)	<p><i>Plans for birth should be made in consultation with the woman, including discussion of the risks and benefits of planned birth <39 weeks', if:</i></p> <ul style="list-style-type: none"> • <i>severe ICP (peak TSBA $\geq 40 \mu\text{mol/L}$ at ≥ 38 weeks'</i> • <i>very severe ICP (peak TSBA $\geq 100 \mu\text{mol/L}$) at ≥ 36 weeks'</i> 	
	<p><i>PT/INR and APTT should be checked in women with severe/very severe ICP (TSBA $\geq 40/\geq 100 \mu\text{mol/L}$), and in women being treated with drugs that inhibit dietary vitamin K uptake, such as cholestyramine and rifampicin. Parenteral vitamin K (10 mg IV) should be administered if either are abnormal. The tests should be repeated weekly until birth, and further parenteral vitamin K administered as indicated.</i></p>	
	<p><i>Outpatient management is recommended if TSBA $< 40 \mu\text{mol/L}$</i></p>	
	<p><i>Outpatient management can be considered if treatment reduces TSBA to $< 40 \mu\text{mol/L}$.</i></p>	
	<p><i>Screen for gestational diabetes (GDM), which is associated with ICP, and consider rescreening after a diagnosis of ICP.</i></p>	
	<p><i>Watch for hypertension and check for proteinuria, given the association of ICP with pre-eclampsia.</i></p>	
MANAGEMENT FETAL ANTENATAL	<p><i>Regular cardiotocography (CTG) monitoring is not required, except when other pregnancy complications (pre-eclampsia and/or GDM and/or fetal growth restriction) are present.</i></p>	

Table 3: Evidence-based recommendations (in bold), Conditional recommendations (in normal type) and Good practice points (in italics) (Continued)

		GRADE: Certainty & Recommendation
MANAGEMENT FETAL ANTENATAL (CONTINUED)	<i>Monitoring fetal growth/wellbeing with serial ultrasounds is not required in the absence of other complications (e.g., GDM and pre-eclampsia).</i>	
	<i>Any decrease/absence of fetal movements is an indication for immediate fetal assessment and CTG.</i>	
MANAGEMENT MATERNAL PERIPARTUM	<i>Admission for assessment and plans for the birth may be considered if TSBA are $\geq 100 \mu\text{mol/L}$, especially after 36 completed weeks of gestation.</i>	
	<i>PT/INR and APTT should be checked in labour in women with severe/very severe ICP (TSBA $\geq 40/\geq 100 \mu\text{mol/L}$), and parenteral vitamin K (10 mg IV) administered if either are abnormal.</i>	
	<i>Active management of the third stage of labour is recommended, given the possible increased risk of postpartum haemorrhage (PPH).</i>	
MANAGEMENT FETAL PERIPARTUM	<i>Continuous electronic fetal monitoring in labour is recommended for women with severe/very severe ICP (TSBA $\geq 40/\geq 100 \mu\text{mol/L}$).</i>	
MANAGEMENT INFANT POSTNATAL	<i>IM Vitamin K should be administered to all neonates of women with ICP, especially if their mothers have been treated with rifampicin⁷³ or cholestyramine⁴⁹.</i>	
MANAGEMENT MATERNAL POSTNATAL	<i>Cease pharmacological treatment at or shortly after birth.</i>	

Table 3: Evidence-based recommendations (in bold), Conditional recommendations (in normal type) and Good practice points (in italics) (Continued)

		GRADE: Certainty & Recommendation
MANAGEMENT MATERNAL POSTNATAL (CONTINUED)	<i>Check TSBA and serum ALT at 6 weeks postnatally. If biochemical abnormalities persist, further investigations should be performed to exclude underlying liver disease.</i>	
	<i>Hormonal contraception is not contraindicated in women who have experienced ICP but, if pruritus recurs in those using hormonal contraception, further investigation should be undertaken. Consideration should be given to using non-hormonal methods of contraception if liver function remains abnormal.</i>	
	Women, who have experienced severe/ very severe ICP, have increased risks of later hepatobiliary disease including liver cancer and require long-term follow-up⁶³. There is as yet no consensus on the follow-up required, but an annual check of liver biochemistry is a reasonable option.	MEDIUM: RECOMMENDATION

Table 4: Classification of evidence levels (GRADE)

- HIGH** Further research is very unlikely to change our confidence in the estimate of effect
- MEDIUM** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- LOW** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- VERY LOW** Any estimate of effect is very uncertain

Grades of recommendations (GRADE)

- STANDARD** At least one meta-analysis, systematic review or randomised controlled trial rated as High and directly applicable to the target population: or
A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as High directly applicable to the target population and demonstrating overall consistency of results
- CONDITIONAL** A body of evidence, including studies rated as Medium or Low, directly applicable to the target population, and demonstrating overall consistency of results
- Good practice points** Recommended best practice based on the clinical experience of the consensus development group.

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