South Australian Perinatal Practice Guideline

Intrahepatic Cholestasis of Pregnancy

Note:

This guideline provides advice of a general nature. This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion.

Information in this statewide guideline is current at the time of publication.

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Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability of the relevant guideline to that clinical situation.

If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom, and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for discussing care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes:

- The use of interpreter services where necessary,
- Advising consumers of their choice and ensuring informed consent is obtained,
- Providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct, and
- Documenting all care in accordance with mandatory and local requirements

Note: The words woman/women/mother/she/her have been used throughout this guideline as most pregnant and birthing people identify with their birth sex. However, for the purpose of this guideline, these terms include people who do not identify as women or mothers, including those with a non-binary identity. All clinicians should ask the pregnant person what their preferred term is and ensure this is communicated to the healthcare team.

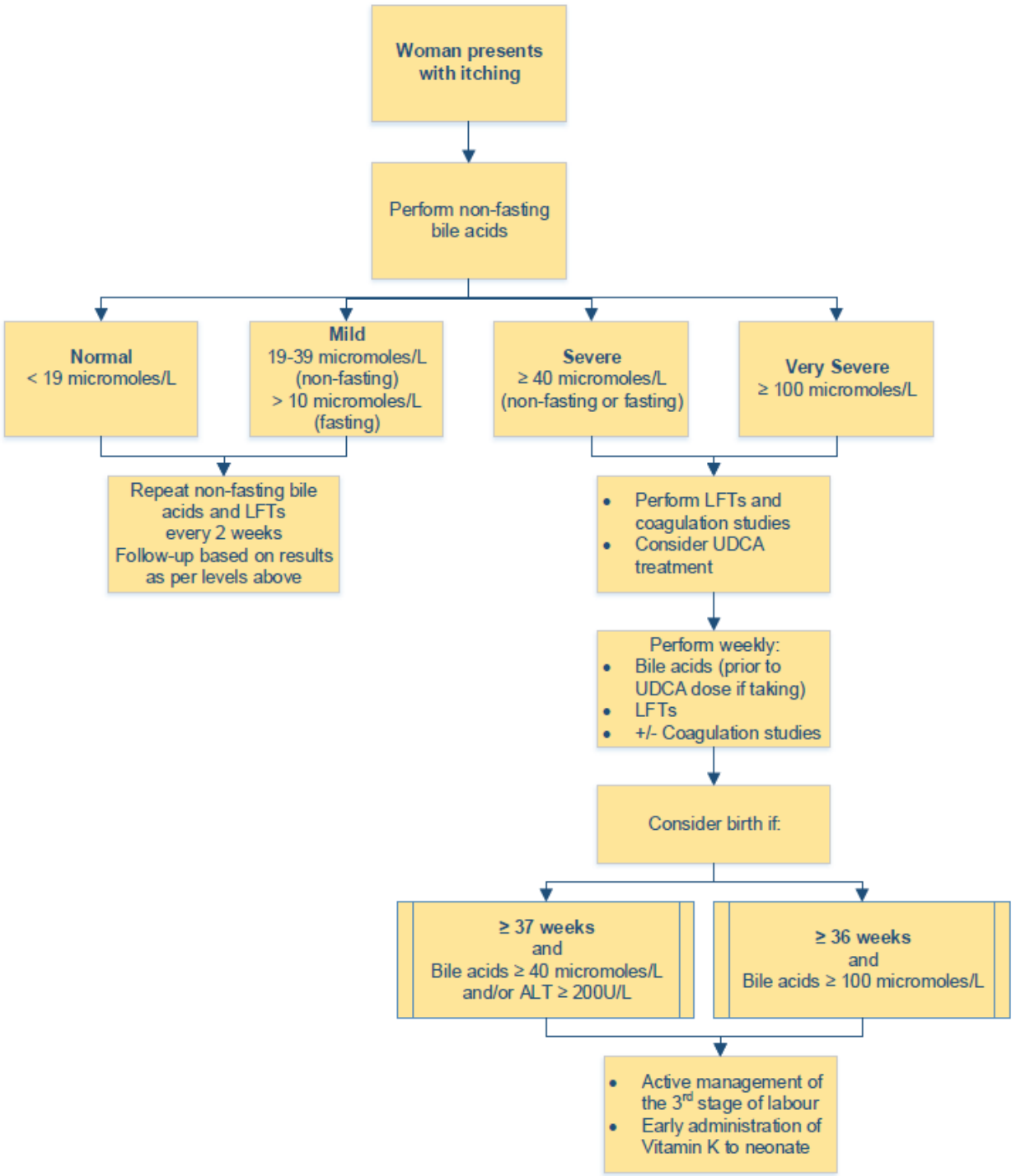
Explanation of the aboriginal artwork:
The Aboriginal artwork used symbolises the connection to country and the circle shape shows the strong relationships amongst families and the Aboriginal culture. The horse shoe shape design shown in front of the generic statement symbolises a woman and those enclosing a smaller horse shoe shape depicts a pregnant woman. The smaller horse shoe shape in this instance represents the unborn child. The artwork shown before the specific statements within the document symbolises a footprint and demonstrates the need to move forward together in unison.

Australian Aboriginal Culture is the oldest living culture in the world yet Aboriginal people continue to experience the poorest health outcomes when compared to non-Aboriginal Australians. In South Australia, Aboriginal women are 2-5 times more likely to die in childbirth and their babies are 2-3 times more likely to be of low birth weight. The accumulative effects of stress, low socio economic status, exposure to violence, historical trauma, culturally unsafe and discriminatory health services and health systems are all major contributors to the disparities in Aboriginal maternal and birthing outcomes. Despite these unacceptable statistics the birth of an Aboriginal baby is a celebration of life and an important cultural event bringing family together in celebration, obligation and responsibility. The diversity between Aboriginal cultures, language and practices differ greatly and so it is imperative that perinatal services prepare to respectfully manage Aboriginal protocol and provide a culturally positive health care experience for Aboriginal people to ensure the best maternal, neonatal and child health outcomes.

Purpose and Scope of Perinatal Practice Guideline (PPG)

This guideline provides clinicians with information on the incidence, diagnosis and management of intrahepatic cholestasis of pregnancy.

Flowchart: Diagnosis and management of ICP



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Summary of Practice Recommendations

Pregnant women who present with itch without a rash should be tested for intrahepatic cholestasis of pregnancy (ICP) with a measure of serum bile acids in non-fasting blood.

- Women with normal (< 19 micromoles/L) or mild ICP (19 – 39 micromoles/L) results should have repeat serum bile acid concentration testing in 2 weeks if itch persists.
- Non-fasting or fasting values greater than or equal to 40 micromoles/L are diagnostic of severe cholestasis.

Non-fasting serum bile acids are preferred as they are more accurate at identifying women with severe ICP than non-fasting tests.

Women with ICP require regular antenatal assessment and review of serum bile acids 2 weekly in the third trimester or mild cases or weekly in severe cases.

Women with severe ICP require urgent referral to an obstetric physician and/or obstetrician.

Consider a plan for birth if:

- diagnosis of severe ICP established at or close to term (≥ 37 weeks)
- diagnosis of very severe ICP (peak serum bile acids ≥ 100 micromoles/L) established at or close to term (≥ 36 weeks)

In the absence of other maternal disorders (e.g. pre-eclampsia and/or gestational diabetes), and with a normally grown fetus, regular cardiotocography (CTG) is not indicated.

Women should be encouraged to report any decrease in fetal movements early to enable timely fetal assessment (see *Decreased Fetal Movements* PPG available at www.sahealth.sa.gov.au/perinatal).

Ursodeoxycholic acid (UDCA) reduces pruritus and improves serum bile acid concentrations and liver function tests (LFTs), and should be considered, particularly if ICP diagnosed preterm.

Treatment with UDCA does not reduce stillbirth or severe perinatal morbidity, but is associated with a reduction in spontaneous preterm birth.

Women being treated with UDCA should have blood drawn for bile acid measurement prior to the morning dose to minimise the measurement of UDCA (itself a bile acid).

Continuous CTG monitoring should be undertaken in labour.

Coagulation studies should be performed in women with severe ICP.

Active management of third stage is encouraged to reduce postpartum haemorrhage risk secondary to malabsorption of vitamin K.

Early administration of vitamin K should be provided to all neonates of women with ICP.

Serum bile acids and liver function should be re-checked at 6 weeks postpartum and, if biochemical abnormalities persist, referral to an obstetric physician or a gastroenterologist/hepatologist should be considered.

Affected women should be advised of a small risk of recurrent symptoms if oral or parenteral contraception is used.

Affected women should be advised that the risk of recurrence in a subsequent pregnancy is between 40% and 92%.

Abbreviations

AFLP	Acute fatty liver of pregnancy
ALT	Alanine transaminase
ALT and AST	aminotransferases
ANA	antinuclear antibodies
APTT	Activated partial thromboplastin time
AST	aspartate aminotransferase
BAs	Bile acids
BRIC	Benign recurrent intrahepatic cholestasis
CMV	Cytomegalovirus
CTG	Cardiotocograph(y)
EBV	Epstein-Barr virus
γGT	gamma glutamyl transferase
GDM	Gestational diabetes mellitus
ICP	Intrahepatic cholestasis of pregnancy
INR	International normalised ratio
IUFD	Intrauterine fetal death
LFTs	Liver function tests
mg	Milligram
NICU	Neonatal intensive care
OGTT	Oral glucose tolerance test
PFIC	Progressive familial intrahepatic cholestasis
PT	Prothrombin time
PUPPP	Pruritic urticarial papules and plaques of pregnancy
RCT	Randomised controlled trial
UDCA	Ursodeoxycholic acid
U/L	Units per litre
µmol/L	Micromoles per litre

Definition

Intrahepatic Cholestasis of pregnancy (ICP)	Previously known as Obstetric cholestasis (OC), ICP is a liver disease of pregnancy (usually in the third trimester) with a complex aetiology including genetic, environmental and endocrine factors.
Mild ICP	Non-fasting serum bile acid concentration 19 - 39 micromoles/L (or fasting values greater than 10 micromoles/L)
Severe ICP	Non-fasting or fasting serum bile acid concentration 40 – 99 micromoles/L
Very severe ICP	Peak serum bile acid concentrations greater than or equal to 100 micromoles/L

Epidemiology

Intrahepatic cholestasis of pregnancy (ICP) is characterised by pruritus without rash (apart from excoriations) and increased concentrations of serum bile acids in pregnancy, and usually with increased concentrations of serum transaminases (occasionally with jaundice) in the absence of other liver pathology, which resolves after birth.[1]

Incidence varies widely, suggesting a geographical and seasonal environmental influence in some populations.

- ICP has been described in up to 24% of indigenous (Araucanian Indian) pregnancies in Chile, although the rate has now fallen to around 1.5 to 4%[2]
- ICP occurs in 1.5% of pregnancies in Scandinavian countries[3]
- ICP occurs in 0.6% of pregnant women in South Australia[4]

ICP

- Is evenly distributed among primigravid and multigravid women
- Is increased five-fold in multiple pregnancies
- May reoccur in subsequent pregnancies of those affected[1,5]
- Has a recognised association with gestational diabetes[3,4,6]
- Has a recognised association with pre-eclampsia[3,4]
- Has an association with gallstones in women and their affected families[7]
- Has an increased incidence in women who are seropositive for hepatitis C, which may be associated with early onset disease[8]

Aetiology and pathogenesis

Intrahepatic cholestasis of pregnancy has a genetic predisposition that influences sensitivity to certain hormonal and environmental factors in the third trimester of pregnancy.[1,2,9] Oestrogen is the most important hormonal precipitant. Intrahepatic cholestasis of pregnancy usually appears when placental oestrogen synthesis is at its highest (third trimester) and resolves soon after birth.[10]

Fetal morbidity and mortality

- Spontaneous preterm labour is more frequent in women with intrahepatic cholestasis of pregnancy, especially if severe (serum bile acids equal to or greater than 40 micromoles/L)[11]
- Severe intrahepatic cholestasis of pregnancy (serum bile acids equal to or greater than 40 micromoles/L) is associated with increased fetal morbidity and mortality[12], including:
    - Preterm birth (25% versus 6.5% in women without ICP)
    - NICU admission (12% versus 5.6% in women without ICP)
- An increased risk for intrauterine fetal death (IUFD) has been identified in affected women with **very severe** intrahepatic cholestasis of pregnancy (serum bile acids equal to or greater than 100 micromoles/L) (Hazard ratio in singleton pregnancy 3·44%; 95% CI 2·05-5·37)[11]
- Stillbirths usually occur after 38 weeks, with little or no warning[13,14]

Clinical presentation

History

- Pruritus (itching) is the cardinal symptom. This usually occurs from around 28 weeks, especially in women with a multiple pregnancy, particularly on the hands and soles of the feet, spreading to the extremities and trunk, without rash (apart from excoriation due to scratching)
- Following initial presentation, pruritus may progressively worsen up until birth, when it rapidly clears
- Sleep disturbance, either due to pruritus or independently, may be severe
- Dark urine, pale stools (uncommon)
- Jaundice ± steatorrhoea (usually 2 – 4 weeks after onset of pruritus) (rare)
- Malaise and anorexia (occasional)
- Previous (although not necessarily all) pregnancies complicated by pruritus
- Past history of gallstones and / or of pruritus while taking the oral contraceptive pill
- Family history of intrahepatic cholestasis of pregnancy or pruritus in pregnancy and/or gallstones

Examination

- Excoriations (scratch marks) may be seen but there are no other typical features
- If a rash is present, consider other diagnoses e.g. polymorphic eruption of pregnancy (although two conditions may rarely co-exist)
- Jaundice is rare

Investigations

There is no single diagnostic test for ICP:

- **Serum total bile acids** are usually increased, and raised non-fasting concentrations equal to or greater than 19 micromoles/L usually confirm the diagnosis in the absence of other hepatic disease.[15] Markedly increased concentrations may be seen in ICP: serum bile acid concentrations equal to or greater than 40 micromoles/L have been associated with increased fetal risk[16], while serum bile acid concentrations equal to or greater than 100 micromoles/L increase the risk of stillbirth[11]. **Recent data, however, suggest that the majority of women with ICP, especially those with mild disease, show a progressive fall in serum bile acids as pregnancy progresses, even without treatment.[17]**
- It is **not necessary** to take fasting blood samples for serum bile acid assay. The important data on fetal wellbeing depend on peak values, irrespective of fasting.[11] The specificity of ICP diagnosis was higher with fasting samples, but the sensitivity was very low (<30%) for mild disease.[15] Should a non-fasting blood sample show the serum bile acid concentration to be less than 19 micromoles/L and liver function otherwise normal, the diagnosis can be considered not proven, and repeat tests can be performed in two weeks to assess progress if itch is continuing[9]. Any non-fasting values equal to or greater than 19 micromoles/L (as well as fasting values, if taken, greater than 10 micromoles/L) can be considered diagnostic of mild cholestasis. Non-fasting (or fasting) values greater than or equal to 40 micromoles/L are diagnostic of severe cholestasis.[18]
- If treatment with ursodeoxycholic acid (UDCA) has been commenced, blood should be drawn for bile acid assay before the morning dose is taken (UDCA is itself a bile acid and may be measured in the assay).[19]
- **Liver function tests (LFTs)**: A rise in serum transaminases (ALT, AST) is usually seen but is not diagnostic.
- Other biochemical disturbances include abnormalities in liver function tests, including gamma glutamyl transferase [γGT] (uncommon, and may reflect a specific subset of women), and bilirubin (rare). Pregnancy ranges must be used.
- **Coagulation studies**: Prothrombin time (INR) and activated partial thromboplastin time (APTT) may be prolonged in severe cases, associated with malabsorption of vitamin K.
- Consider **upper abdominal ultrasound** to exclude obstructive gallbladder disease and establish gallstones
- **Liver biopsy** is not usually necessary

Note: Normal values for serum bile acids and transaminases may occasionally be seen, with progression to abnormal values over time[20]. Women with persisting pruritus and normal bile acids / ALT should have repeat tests every 2 weeks.

Differential diagnosis

- Check for any pre-existing liver disease, alcohol or other drug dependence
- Consider viral hepatitis (especially if jaundice and dark urine present): check viral serology, including hepatitis A, hepatitis B, hepatitis C, cytomegalovirus (CMV) and Epstein-Barr virus (EBV).[13] Intrahepatic cholestasis of pregnancy is more common and may present early in women with chronic hepatitis C infection[8]
- Previous childhood jaundice with pruritus (non-infective and post-neonatal) and oral contraceptive related pruritus and/or jaundice raise the possibility of genetic causes of cholestasis, such as benign recurrent intrahepatic cholestasis (BRIC) and progressive familial intrahepatic cholestasis (PFIC)

- Autoimmune liver disease may rarely present in pregnancy, but should be considered, especially if there is a family history of autoimmune disorder (thyroid, rheumatoid, etc.). Anti-smooth muscle and anti-LKM antibodies (chronic hepatitis), and anti-mitochondrial antibodies (primary biliary cholangitis), together with antinuclear antibodies (ANA), should be checked in women presenting with severe or early-onset disease.
- Pruritic urticarial papules and plaques of pregnancy (PUPPP syndrome or polymorphic eruption of pregnancy) and papular dermatitis of pregnancy have accompanying papules and plaques with itching. They may rarely co-exist with intrahepatic cholestasis of pregnancy.
- Pre-eclampsia and acute fatty liver of pregnancy (AFLP) are pregnancy-specific causes of abnormal LFTs and need to be considered in the differential diagnosis. These diseases can coexist with cholestasis, and pre-eclampsia is up to ten times more common in women with intrahepatic cholestasis of pregnancy[4]
- Gestational diabetes is three times more common in women with intrahepatic cholestasis of pregnancy[4]

Antenatal Management

Once a diagnosis of ICP is established, regular assessment and review of serum bile acids should be initiated two weekly in the third trimester for mild ICP (serum bile acids 19-39 micromoles/L), or weekly in severe cases (serum bile acids ≥ 40 micromoles/L).

Discuss with obstetric physician and/or obstetrician following diagnosis of ICP and arrange urgent referral and consult/transfer of care in severe cases (serum bile acids ≥ 40 micromoles/L).

Consider ongoing care at a tertiary hospital for early onset cases, especially if severe.

Plan birth in consultation with the woman (including discussion of the risks and benefits of planned birth < 39 weeks) if:

- diagnosis of severe ICP (peak serum bile acids equal to or greater than 40 micromoles/L) established at or close to term (≥ 37 weeks)
- diagnosis of very severe ICP (peak serum bile acids equal to or greater than 100 micromoles/L) established at or close to term (≥ 36 weeks)

Antenatal admission

Outpatient management is recommended if:

- Serum bile acids less than 40 micromoles/L
- Alanine aminotransferase (ALT) less than 200 units/L

Admission for assessment, though not essential, may be considered if serum bile acids equal to or greater than 40 micromoles/L or ALT greater than 200 units/L and if the woman is remote from obstetric care, and/or if there are other pathologies, such as pre-eclampsia.

Recommend admission for assessment and making plans for birth if serum bile acids equal to or greater than 100 micromoles/L, especially approaching term.

Further outpatient management can be considered if treatment reduces the serum bile acids to less than 40 micromoles/L or if there is stability or reduction in the serum ALT, remote from term.

Fetal surveillance

In the absence of other maternal disorders (for example pre-eclampsia and/or gestational diabetes), and with a normally grown fetus, regular CTG monitoring is not required. Earlier 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 in the hours before the diagnosis of IUFD associated with ICP.[19,20]

Any decrease / absence of fetal movements should be reported as soon as possible and is an indication for fetal assessment and CTG (see *Decreased Fetal Movements* PPG available at www.sahealth.sa.gov.au/perinatal)

Umbilical artery Doppler measurements do not seem to have any predictive value for stillbirth with a normally grown fetus without other complications in the context of ICP.[21]

Pharmacological management

Ursodeoxycholic acid (UDCA)

UDCA has been shown to reduce pruritus; however, **the degree of benefit may be small**.[17] UDCA treatment has also shown benefit in small improvements in serum bile acid concentrations and measurements of liver function in intrahepatic cholestasis of pregnancy[17], but it should be noted that there was a spontaneous fall in serum bile acid concentrations in the placebo arm.

Randomised data in individual trials have shown no fetal benefit with UDCA, with no reduction in stillbirth or severe perinatal morbidity[17], although there are no established adverse effects of the drug on fetal / neonatal safety.

However, a recent individual patient data meta-analysis of UDCA treatment in 34 studies, (including 4 randomised controlled trials [RCTs]), has shown that in the RCTs, UDCA treatment was associated with a 40% reduction of the composite outcome of stillbirth and preterm birth (p=0.016), predominantly due to reduced spontaneous preterm birth; there was no statistically significant effect on stillbirth. Analysis of aggregate data from published RCTs has revealed a 45% reduction in total preterm birth with UDCA treatment (p<0.001).[22,23]

Use of UDCA should therefore be considered if intrahepatic cholestasis of pregnancy is diagnosed remote from term to improve maternal symptoms and liver function, and to help reduce some serious adverse pregnancy outcomes:

- Start with 250 mg three times a day in mild cases, 500 mg three times a day in severe cholestasis (serum bile acids greater than 40 micromoles/L) and increase up to 500 mg four times a day (20 mg / kg), depending on symptoms and biochemistry

Other agents

- Women who fail to respond to UDCA may be considered for treatment with additional rifampicin (300 mg twice a day), a recognised inducer of liver enzyme metabolism.[24]
- Some agents (including activated charcoal and cholestyramine) have been used to bind bile acids in the intestine, thus reducing uptake. These agents have potential adverse effects for mothers due to the depletion of vitamin K, required for blood clotting, so parenteral Vitamin K may be necessary.[25] Further trials are required before any firm conclusions can be made about the effectiveness of these and other agents in pregnant women with severe cholestasis.[25]
- Antihistamines, e.g. cetirizine 10 mg one to two times a day according to medical prescription and/or promethazine 25 mg at night according to medical prescription, may be useful in relieving pruritus.
- Vitamin K 10 mg daily orally, or 10 mg weekly as an intravenous injection, if prolonged prothrombin and/or activated partial thromboplastin times, or if the woman develops steatorrhea.
- Consider plain sorbolene lotion, Pinetarsol solution, aqueous cream with 2% menthol, or bicarbonate of soda baths for symptomatic relief.

Ongoing investigations

- 2 weekly measurement of serum bile acids in mild cases or where pruritus persists; at least weekly in severe cases (serum bile acids equal to or greater than 40 micromoles/L)
- 2 weekly measurement of serum transaminases (ALT) in mild cases; at least weekly in severe cases (serum bile acids equal to or greater than 40 micromoles/L)
- Coagulation studies after diagnosis of severe cholestasis (serum bile acids equal to or greater than 40 micromoles/L) and before induction of labour (may be prolonged PT / INR and/or APTT)

Intrapartum management[26]

- Consider birth at:
  - 37-38 weeks if serum bile acids and LFTs remain high (bile acids equal to or greater than 40 micromoles/L or ALT greater than 200 units/L)
  - 36-37 weeks if bile acids remain equal to or greater than 100 micromoles/L
- Continuous electronic fetal monitoring in labour should be used
- Coagulation studies to check PT, INR and APTT in severe cholestasis (serum bile acids equal to or greater than 40 micromoles/L)
- Active management of third stage is recommended (increased risk of postpartum haemorrhage secondary to malabsorption of vitamin K)
- Ensure early administration of vitamin K to all neonates of women with ICP, especially if the mothers have been treated with rifampicin

Postpartum management

- Pruritus will usually disappear 1-2 days after birth
- Jaundice usually resolves in the first week
- Serum bile acid concentrations should normalise within the first week
- Check bile acids and liver function at 6 weeks postpartum, e.g. at the time of an OGTT if there has also been GDM
- Exclude underlying liver disease if biochemical abnormalities persist beyond 6 weeks postpartum

Counselling

- Risk of recurrence in a subsequent pregnancy is 40 to 92%.
- Inform the woman that there are few data on long term sequelae for the baby: one small study has suggested an increase in serum lipids at age 16 years, associated with an increase in body mass index in males and in abdominal girth in females.[27]
- Women who have had severe familial intrahepatic cholestasis of pregnancy are, however, at risk of chronic liver disease and should have long-term follow-up.
- Female family members have an increased risk of intrahepatic cholestasis of pregnancy.

Follow up

- General practitioner review at 6-8 weeks postpartum to check bile acids and liver function, and glucose tolerance testing for those women who also had GDM
- 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 and consideration given to using other methods of contraception if the liver function is abnormal
- Physician review at 2-3 months postpartum if any biochemical abnormalities persist

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

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