



Intrahepatic Cholestasis of Pregnancy

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**Course Description:**

This course focuses on participants gaining a better understanding of Intrahepatic Cholestasis of Pregnancy (ICP), early recognition of women affected by this condition, and the issues it brings to a woman and her unborn fetus.

Approximate Time to Complete: 55 minutes



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print version of this course.*



Introduction





The course will:

- Help participants develop sound clinical judgment in the delivery of health care when concerns are suspected in regards to Intrahepatic Cholestasis of Pregnancy (ICP).
- Expand participant's knowledge base on learning theories and their instructional implications regarding health care for delivery and postpartum when ICP is questionable.
- Help participants provide implementation of the necessary steps needed when fetal well-being is questionable.
- Enable participants to convert proven learning into actual health care delivery.





-  Introduction
-  Etiology and Risk Factors
-  Patient Presentation
-  Physical Exam
-  Laboratory Findings
-  Ultrasound
-  Pathology
-  Differential Diagnosis
-  Diagnosis
-  Fetal Complications
-  Maternal Treatment
-  Pregnancy Management
-  ICP Guidelines
-  ICP Delivery Recommendations
-  Postpartum Maternal Management
-  Postpartum Monitoring
-  Postpartum Contraception
-  Planning and Prevention
-  Summary and Recommendations



Intrahepatic Cholestasis of Pregnancy (ICP) Definition

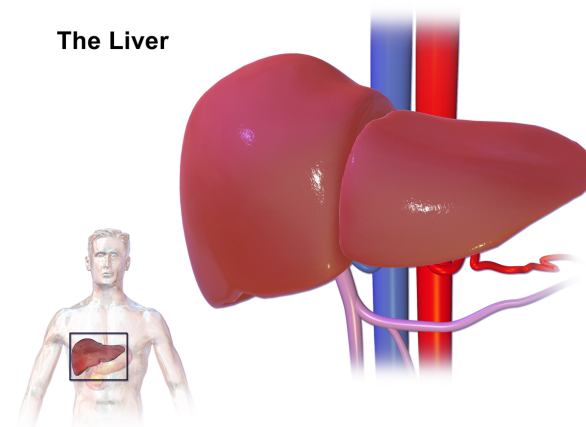
ICP is diagnosed based on pruritus and elevation in serum bile acid concentrations. This condition generally develops in the late second and/or third trimester of pregnancy.

However, cases have been reported as early as 8 weeks of pregnancy and moderate itching at any point in pregnancy should not be ignored.

The incidence rate varies worldwide, from <1 to 27.6%. It is thought the differences among population groups and environmental factors may contribute to the incidence rates [\[4, 5\]](#).



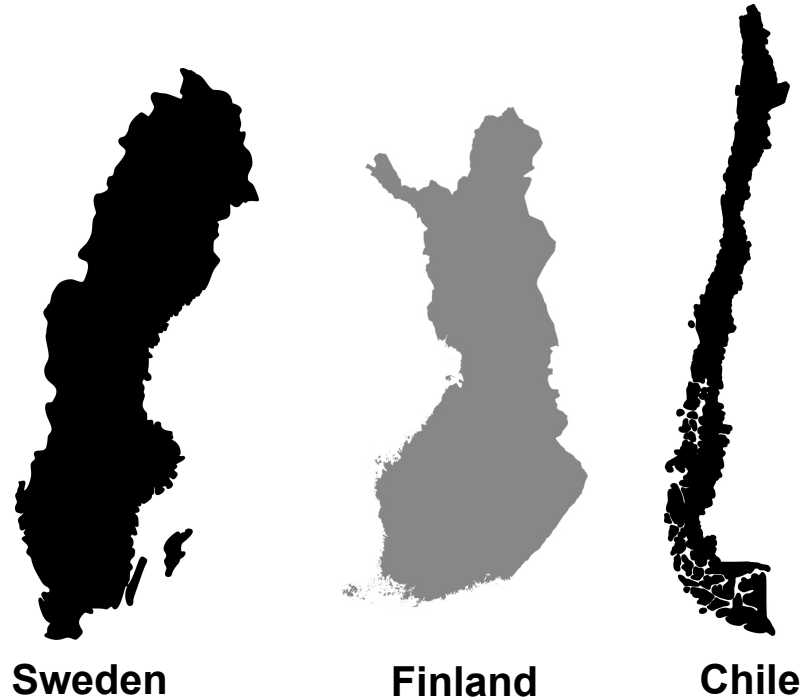
Definition



Incidence of ICP

It is not clearly understood, but the disease commonly occurs in the winter months in the countries of Sweden, Finland, and Chile [2].

It is also more common in multiple gestations with the highest risk associated with higher order multiple gestations [8].



Finland - Single Color by FreeVectorMaps.com

Incidence of ICP





In Chile, 27.6% of Araucanos Indians are affected with ICP, representing the highest incident rate worldwide [4].

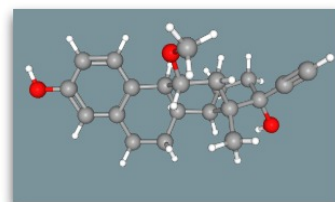


In the United States, the occurrence rate is from 0.32% of women in Bridgeport Hospital, Connecticut to 5.6% in a Hispanic population in Los Angeles, California [6, 7].





Genetic Susceptibility



Hormonal Factors



Environmental Factors

The etiology of ICP is not clearly understood; however, a combination of the following risk factors are suspected:

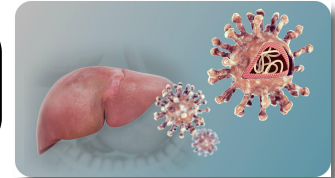
National Center for Biotechnology Information. PubChem Database. Moxestrolum, CID=71714, <https://pubchem.ncbi.nlm.nih.gov/compound/Moxestrolum> (accessed on Nov. 10, 2019) [Source link](#)



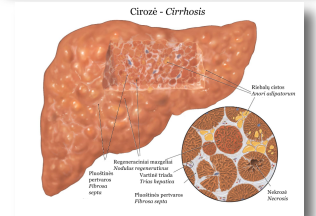
Additional Risk Factors

Other factors that affect the incident rate include [11]:

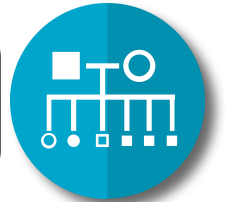
Personal history of chronic hepatitis C



Personal history of nonalcohol liver cirrhosis



Prior personal history or family history of intrahepatic cholestasis



Advanced maternal age





A woman who has had ICP has a 60 to 70% risk of recurrence in subsequent pregnancies. The severity varies in subsequent pregnancies.



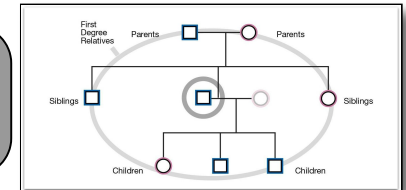
Etiology - Genetic Susceptibility

The genetic cause of ICP is very complicated, but genetic susceptibility in evidence demonstrates [12]:

Familial Clustering



Increased risk in first-degree relatives



Increased risk in some ethnic groups



Recurrence rate of 60-70% in subsequent pregnancies



Etiology - Genetic Susceptibility

PFIC3 is a familial form of ICP and has been associated with the a mutation in the ABCB4 gene.

- 16% of Caucasian patients with ICP have the ABCB4 gene mutation [[22](#)].
- Numerous heterozygous mutations in the ABCB4 gene were reported in women with ICP [[16](#),[86](#)].
- Other genes possibly involved in ICP pathogenesis include ABCB11, ATP8B1, ABCC2, NR1H4 [[16](#), [17](#), [18](#), [19](#), [20](#), [22](#), [23](#), [86](#)].





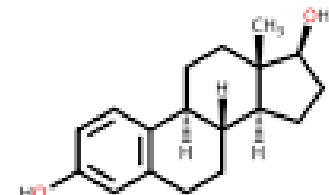
Etiology - Hormone Effect in ICP

Estrogen [21, 22]

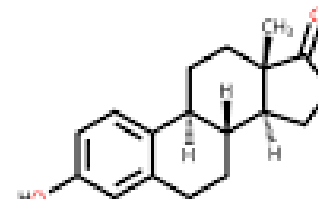
In experimental and clinical studies, estrogen has been associated with ICP.

- Serum estrogen reaches peak levels in the second half of pregnancy when ICP is noted to occur.
- Serum estrogen levels are higher in multiple gestation when compared to singleton pregnancies. This supports findings that ICP occurs more often at higher rates in multiple gestation.

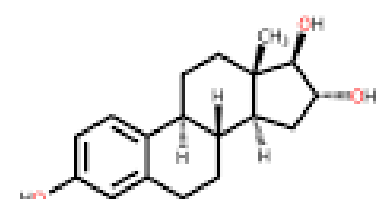
ESTROGENS



Estradiol



Estrone



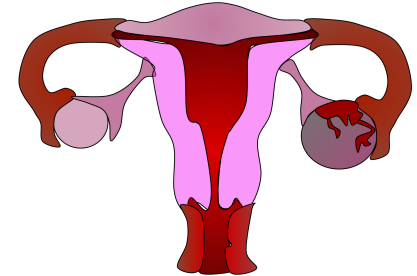
Estriol





Etiology - Hormone Effect in ICP

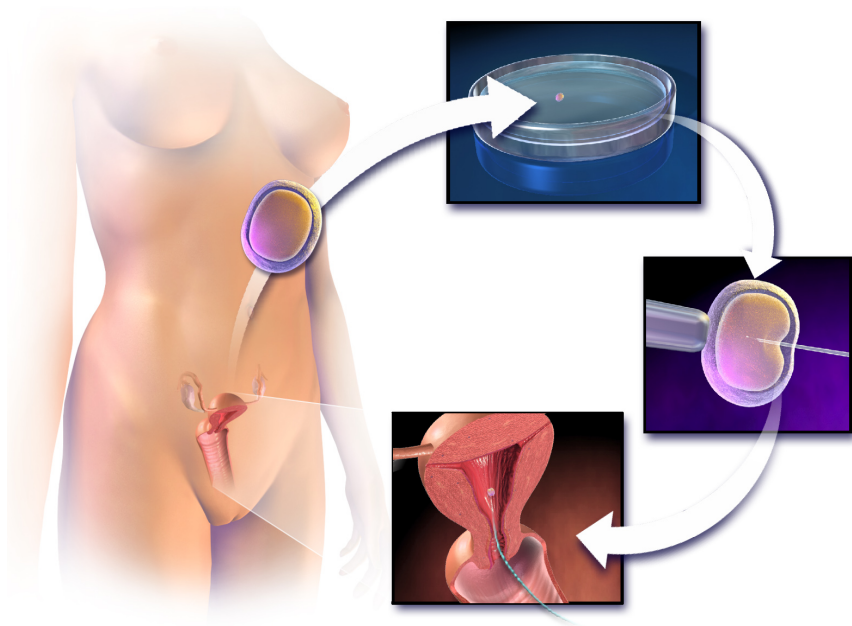
ICP has been seen earlier in pregnancy following ovarian hyperstimulation, probably related to the considerably high serum estrogen level.



The placenta is the major source of estrogen production during pregnancy in the second and third trimester, which is likely why ICP resolves after delivery of the placenta.



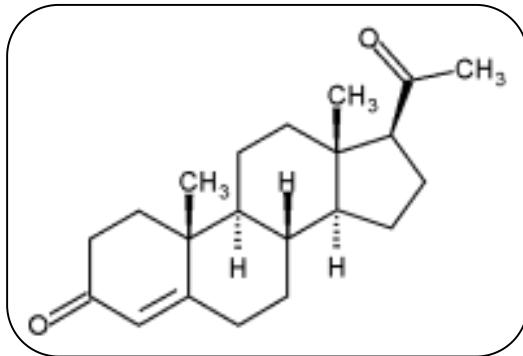
Etiology - Special Populations and Hormone Effects



Transient symptoms of cholestasis may be seen in women with a history of cholestasis undergoing ovarian stimulation for in vitro fertilization due to high estrogen levels.

Etiology - Hormone Effect in ICP

Progesterone metabolism may contribute to the pathogenesis of ICP.

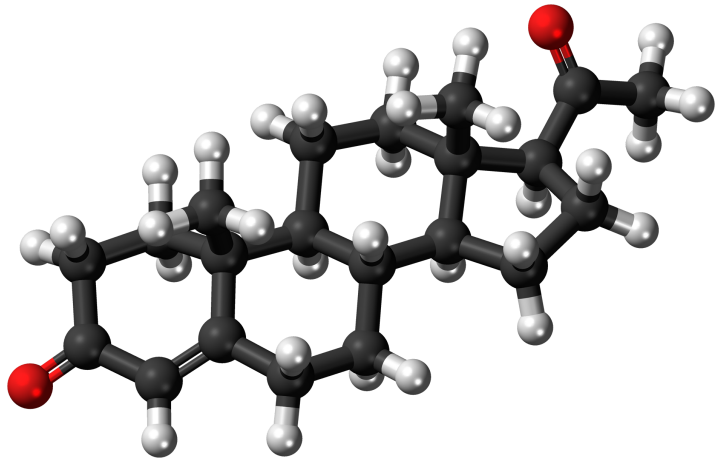


Progesterone

Progesterone

- In women who are genetically predisposed, the development of large amounts of sulfated progesterone metabolites in pregnancy may result in saturation of the hepatic transport used for biliary excretion of these compounds [[23](#), [24](#)].

Etiology - Hormone Effect in ICP



Progesterone

- It is not known if administration of exogenous progesterone during pregnancy increases the risk of ICP.
- Progesterone supplementation for reducing the risk of spontaneous preterm birth (PTB) was not associated with an increased rate of ICP in a placebo-controlled randomized trial [\[32\]](#).



Etiology - Special Populations and Hormone Effects

- It is uncertain if providing progesterone supplementation to women with a history of previous PTB or a short cervical length in the current pregnancy should be avoided if she has a previous history of ICP.
- The decision of whether or not to initiate supplemental progesterone in a pregnancy should be individualized based on risks and benefits.

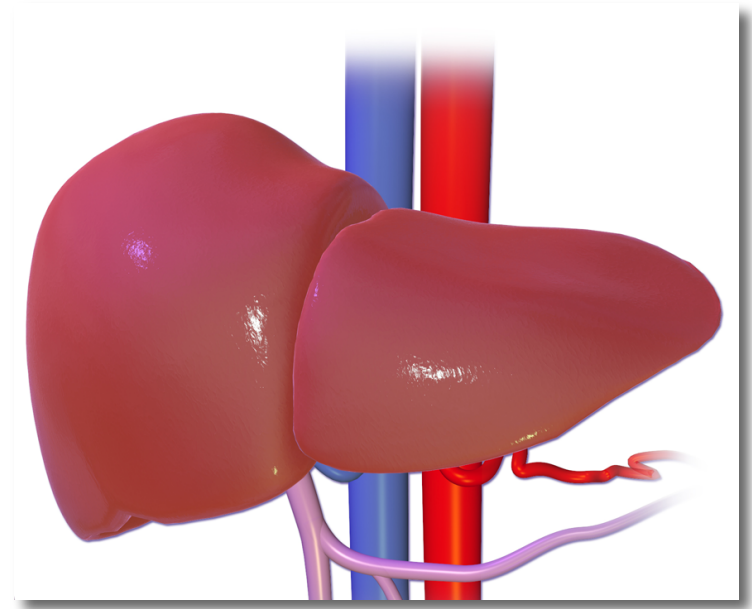


Etiology- Environmental Factors in ICP

- Seasonal and geographic variables influence the expression of the disease.
- Low selenium levels related to dietary deficiency and low vitamin D levels due to lack of sunlight exposure have been suspected causative factors [[11](#), [33](#)].

Etiology - Underlying Liver Disease

- Liver disease has been identified in a small number of women who develop ICP [[27-30](#)].
- Hepatitis C and nonalcoholic liver cirrhosis are associated with increased risk of ICP [[28](#)].





ICP Clinical Presentation

Women with ICP may present with mild to unbearable pruritus. Pruritus may be generalized, but usually starts on the soles of the feet and the palms of the hands.

Pruritis is usually worse at night.



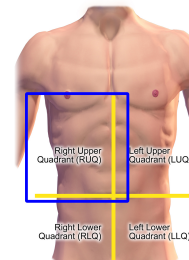


ICP Clinical Presentation



Click on the pictures for
other ICP symptoms
that may occur

Nausea



Abdominopelvic
Quadrants

Right
Upper
Quadrant
Pain

Sleep
Deprivation



Oily Stools



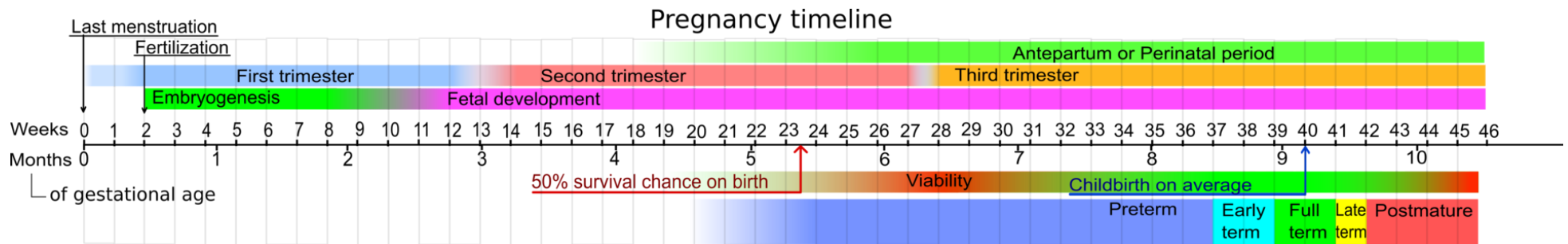
Poor Appetite



ICP Patient Presentation

Consider these symptoms at the different stages of pregnancy:

- Symptoms of ICP may be transient in the first trimester in women who have encountered ovarian hyperstimulation after in vitro fertilization [22].
- Symptoms that are persistent and worsening occur in women who have naturally conceived [31].
- Pruritus and other symptoms usually develop during the late 2nd or 3rd trimester.
- The causes of liver disease should be evaluated in women who develop encephalopathy or other stigmata of liver failure.



ICP Physical Examination

- Women with ICP most commonly have no physical manifestations of the disease.
- Typically, if a rash is present, alternative diagnoses should be investigated.
- In severe cases, women with pruritis may present with scratch marks and excoriations. Prurigo nodules may occur secondary to scratching.



ICP Physical Examination

In women with ICP, 14 to 25% will develop jaundice. Jaundice generally develops one to four weeks after the itching begins [32].

Other causes of jaundice should be determined if there is no pruritus.



ICP Laboratory Findings

The normal physiological changes that occur in pregnancy must be considered when performing a workup of abnormal liver tests in a pregnant woman [[85](#)].



ICP is diagnosed based on elevated serum bile acids. Women may also have elevated liver transaminases [[25](#), [33](#), [34](#)].

Pruritis may occur prior to the development of lab abnormalities [[35](#)].



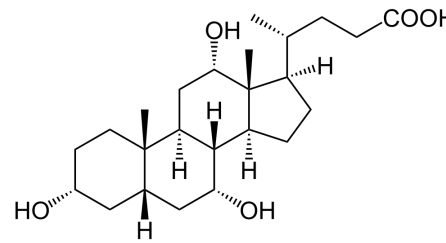
Click the silhouette for more information.



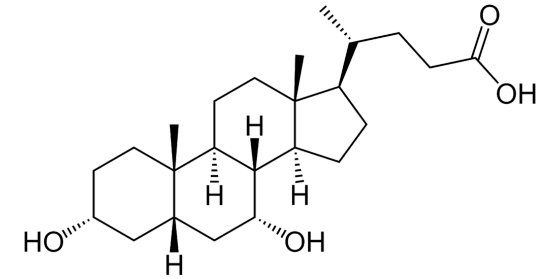


ICP Laboratory Findings

The normal physiological changes that occur in pregnancy must be considered when performing a workup of abnormal liver tests in a pregnant woman [\[85\]](#).



cholic acid



chenodeoxycholic acid

Cholic and chenodeoxycholic acids are the primary bile acids that are increased, but cholic acid increases more than chenodeoxycholic acid which causes an increased ratio [\[32, 35, 37\]](#). A ratio of these two acids is not necessary to diagnose ICP [\[38\]](#).





Other possible laboratory findings include:

Serum
Aminotransferase
(AST) and Alanine
Aminotransferase
(ALT)

AST and ALT increases in 60% of cases. These increases are usually less than two times the upper limit of normal, but may reach levels over 1000 unit/L which should prompt evaluation of viral hepatitis [\[32\]](#).

Bilirubin

25% of ICP cases have increases in total and direct bilirubin concentrations. However, total bilirubin levels do not generally increase greater than 6mg/dL.

Gamma-glutamyl
transpeptidase
(GGT)

GGT is normal or mildly increased in 30% of ICP cases. GGT levels align with other cholestatic markers in other forms of cholestatic liver disease helping to make the diagnosis of ICP or other causes for the increase.



Click on the rectangles for more information

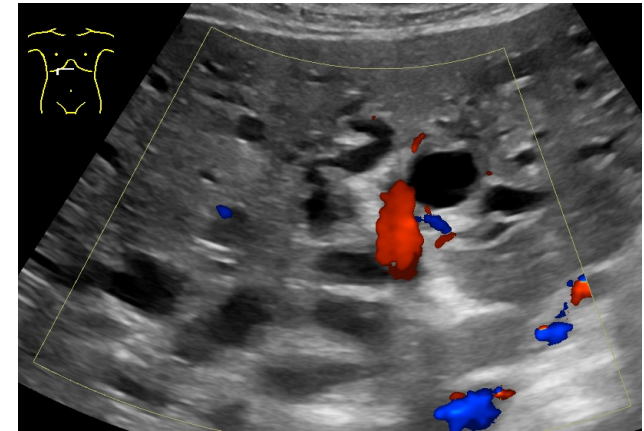




Hepatic Ultrasound

Ultrasonography is not necessary in diagnosing ICP.

- Women with ICP do not have abnormal findings on hepatic ultrasound.
- Biliary ducts are not dilated.
- Hepatic parenchyma appears normal.
- Hepatic ultrasound can be considered to rule out any underlying liver conditions in women with early onset or severe cholestasis.



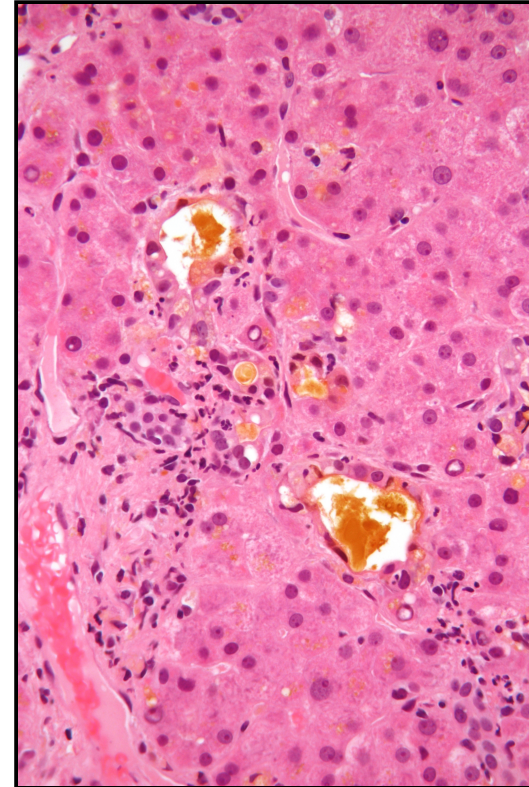
Ultrasound of dilated bile ducts





ICP Pathology

Histopathology is rarely available as liver biopsy is not necessary for diagnosis of ICP.



Cholestasis 2 - High Magnification





Differential Diagnosis of Liver Dysfunction

Pregnancy specific causes of hepatic impairment:

- Acute fatty liver of pregnancy
- Hemolysis, elevated liver enzymes and low platelets syndrome (HELLP)
- Hyperemesis gravidarum
- Primary biliary cirrhosis (shown above) or primary sclerosing cholangitis
- Viral hepatitis
- Autoimmune hepatitis
- Drug-induced liver injury
- Biliary obstruction
- Venocclusive disease



Differential Diagnosis of Pruritis

Pruritus and hepatic dysfunction possible causes:

- | | |
|--------------------------------------|-----------------------------|
| • Pruritus gravidarum | • Atopic dermatitis |
| • Atopic eruption of pregnancy | • Allergic or drug reaction |
| • Polymorphic eruption of pregnancy | • Systemic disease |
| • Pemphigoid gestationis | • Atopic dermatitis |
| • Prurigo of pregnancy | • Allergic or drug reaction |
| • Pruritic folliculitis of pregnancy | • Systemic disease |



Differential Diagnosis



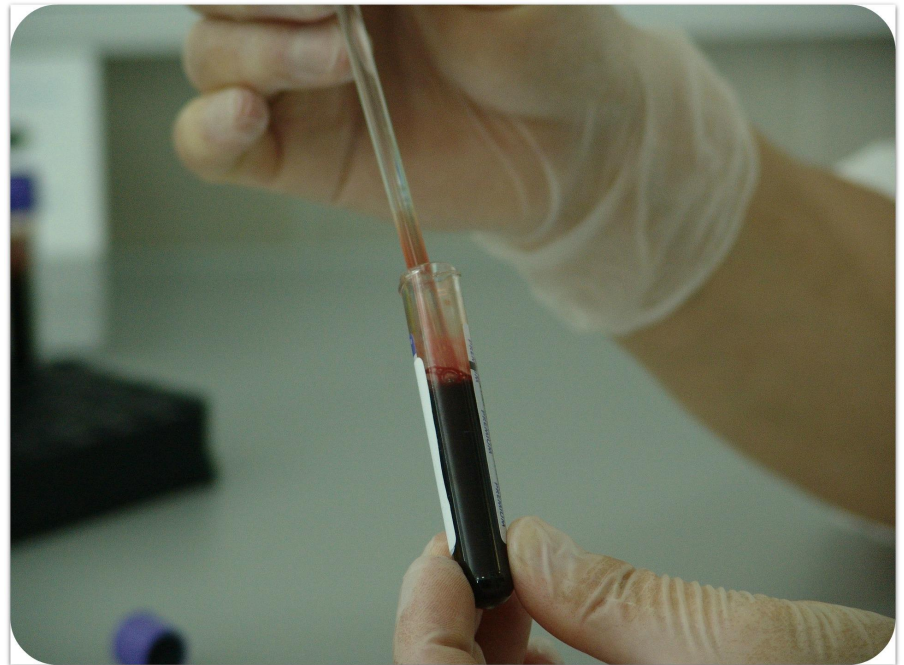
- Pruritus is the cardinal sign of ICP is not typically present in:
 - HELLP syndrome
 - Preeclampsia with severe features
 - Acute fatty liver of pregnancy
- Pruritus occurs in 23% of pregnancies [\[81\]](#).
- ICP does not present with primary skin lesions which helps distinguish it from:
 - Pregnancy-specific pruritic dermatoses
 - Skin conditions unrelated to pregnancy



ICP Diagnosis

Diagnosis is based upon [\[84\]](#):

- Pruritus
- Elevated bile acids

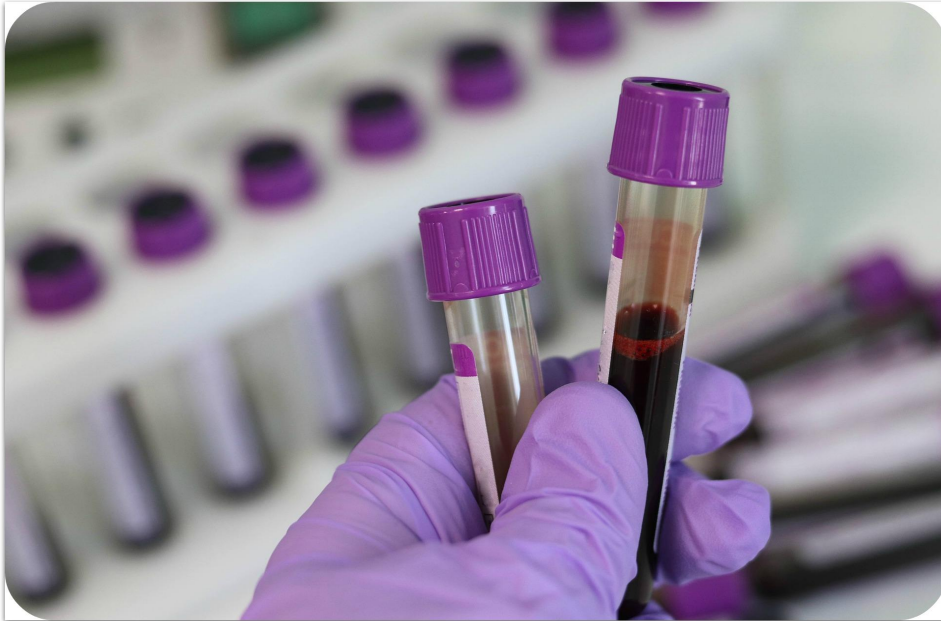


ICP Diagnosis

- A total serum bile acid level of >10 $\mu\text{mol/L}$ is typically used to diagnose ICP
- There is some variance in laboratory reference ranges, which results in different values for the upper limit of normal
- Any bile acid value above the upper limit of normal is diagnostic of ICP
- Elevated transaminases can sometimes be seen in ICP; however, they are not diagnostic
- If a woman presents with new onset pruritis at term and elevated transaminases are noted; it is not necessary to await confirmation of the diagnosis with bile acids [\[75\]](#).



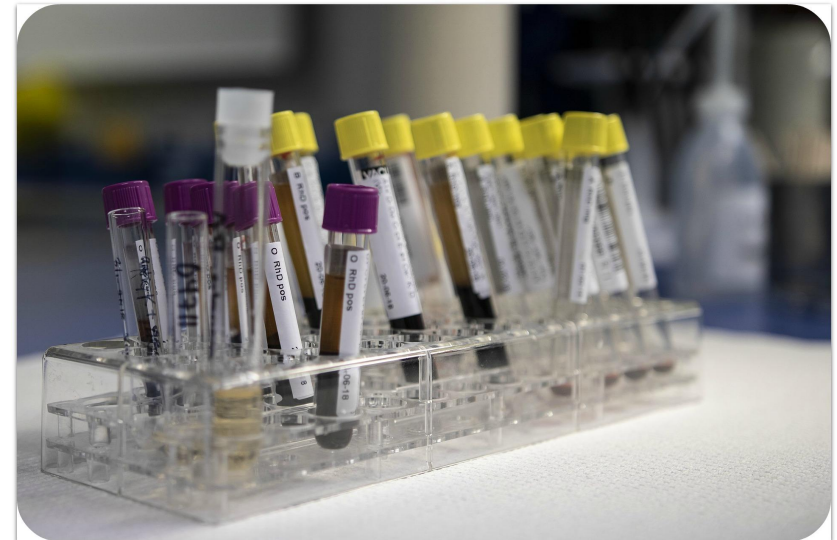
ICP Diagnosis



- Trimester specific reference ranges for Total Serum Bile Acid (TSBA) should be used to determine if elevated.
- If trimester specific ranges are not available in the lab, then general population values are used.

ICP Diagnosis

- TSBA ranges vary due to laboratory methods and are dependent on fasting levels. Bile acids are typically slightly higher in a non-fasting state [[39](#), [40](#)].
- It is recommended to repeat laboratory tests weekly if total bile acid and aminotransferase levels are initially normal because pruritus can precede the rise in serum bile acids by many weeks.
- Given this lag in laboratory confirmation, it is not recommended to start ursodeoxycholic acid (UDCA, ursodiol or Actigall®) until the diagnosis is confirmed.





ICP Fetal Complications

Transplacental gradients facilitate fetal clearance of bile acids in normal pregnancies [\[25, 42\]](#).



Bile acid leaves the fetus



ICP Fetal Complications

Transplacental gradients facilitate fetal clearance of bile acids in normal pregnancies [25, 42].

In pregnancies affected by ICP, the transplacental gradient is reversed and an accumulation of bile acids occurs in the amniotic fluid and fetus [43].

ICP is associated with increased risk of [83,44]:

- Intrauterine fetal demise (IUFD)
- Meconium-stained amniotic fluid
- Spontaneous preterm birth
- Iatrogenic preterm birth
- Neonatal respiratory distress syndrome (RDS)
- Neonatal intensive care unit (NICU) admissions

Bile acid accumulates

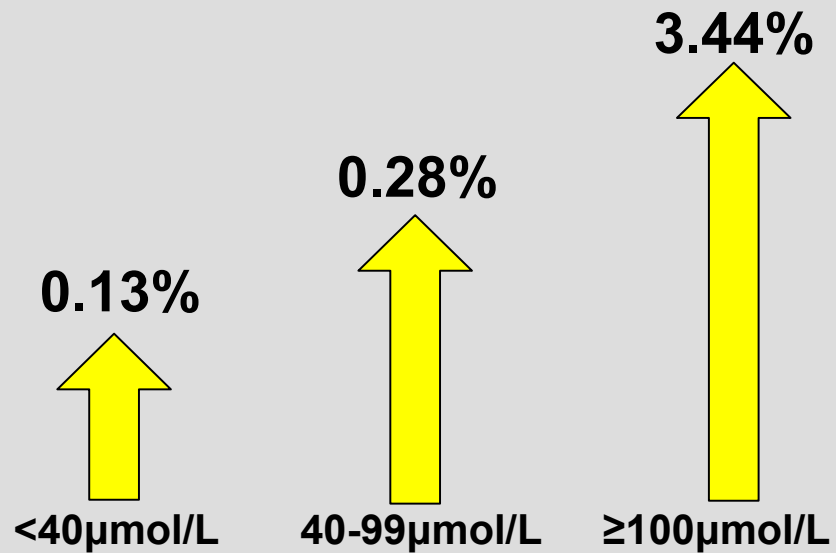




ICP Fetal Complications

Fetal demise increases when the maternal bile acid level is higher, particularly when $\geq 100\mu\text{mol/L}$.

The arrows point to the risk of fetal demise based upon bile acid levels.



1 of 3 >>





ICP Fetal Complications

- The rate of stillbirth after 37 weeks gestation is estimated at 1.2%.

◀ 2 of 3 ▶





ICP Fetal Complications

Please note that these outcomes occurred due to early delivery and from ursodiol treatment. The women from this study were actively managed by ICP treatment guidelines. These would certainly NOT be the rates if women with ICP were not treated and completed 40 weeks of gestation. The fetal death rate would be terrorizing to all of us in healthcare in this later situation.

◀◀ 3 of 3





ICP Fetal Complications

Fetal death in ICP is NOT clearly understood but is believed to be induced by high levels of bile acids causing:

- Sudden development of fetal arrhythmia [45]
- Vasospasm of the placental chorionic surface vessels [46]
- Concurrent pregnancy complications such as gestational diabetes or preeclampsia [47]



1 of 3 >>



ICP Fetal Complications

Bile acids increase expression of myometrial oxytocin receptors, which is believed to be associated with spontaneous preterm labor. Pregnancies complicated by ICP and preterm labor tend to have an earlier onset of pruritis [[48](#), [49](#), [50](#)].



2 of 3 >>



ICP Fetal Complications

Features not associated with ICP [\[25\]](#)

- Oligohydramnios
- Fetal growth restriction



3 of 3

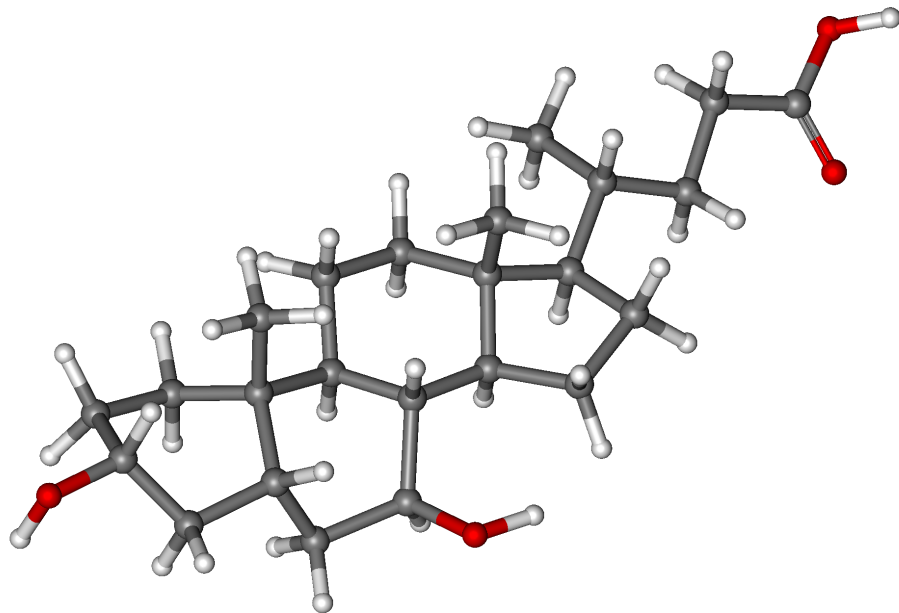
ICP Treatment



- Treatment is indicated to reduce maternal symptoms of pruritis and potentially to improve pregnancy outcomes.
- Treatment should not be initiated until the diagnosis is confirmed.



ICP Treatment



The preferred medication for treatment of maternal pruritus due to ICP is Ursodeoxycholic acid (UDCA) (*Shown on the left*) [51]. No additional lab testing is needed prior to initiating UDCA other than those drawn for diagnosis of ICP.

Pruritis is generally decreased in 1 to 2 weeks after initiation of UDCA.





ICP Treatment



- Typical UDCA initial doses include [\[80\]](#):
 - 10-15 mg/kg per day, divided into 2 or 3 doses
 - 300 mg BID or TID
 - 500 mg BID
- If pruritus is not decreased in 2 weeks of starting UDCA, the dose can be increased to a maximum of 21mg/kg per day [\[52,53,54,55\]](#).





ICP Treatment

- UDCA is tolerated well by most women; however, 25% of women may develop mild nausea and dizziness.
- Following the initiation of UDCA, maternal bile acid levels should be monitored because significantly increased risk of stillbirth is noted when maternal concentrations $\geq 100\mu\text{mole/L}$ [\[44\]](#).
- Improvement in lab results is seen in 3 to 4 weeks.
- UDCA can be discontinued when labor begins if used for management of ICP symptoms.





ICP Treatment

If the woman continues to have symptoms despite treatment with UDCA, additional therapy can include [\[60,61\]](#):

- S-adenosyl-methionine
- Cholestyramine
- Rifampin
- Hydroxyzine
- Diphenhydramine

These medications are not as effective as UDCA, but can be considered for patients who cannot take UDCA or whose symptoms are refractory to treatment.





ICP Treatment if UDCA Alone is Ineffective

S-adenosyl-methionine (SAME):

- SAME is a glutathione precursor and influences the composition and fluidity of hepatocyte plasma membranes. In addition, SAME increases the methylation and biliary excretion of hormone metabolites [\[56\]](#).
- In a meta-analysis of five randomized trials of 311 pregnant women, UDCA at a dose of 450 to 1000mg/day decreased the pruritus score, total bile acids, and alanine aminotransferase levels more effectively than SAME 800 to 1000mg/day [\[57\]](#).
- SAME is administered intravenously (IV) which is inconvenient when used for long term therapy. SAME 1600mg/day orally has been used to treat cholestasis in nonpregnant patients [\[58\]](#).



ICP Treatment if UDCA Alone is Ineffective



Cholestyramine

- Cholestyramine decreases ileal absorption of bile salts which increases their fecal excretion.
- Cholestyramine effect of pruritus in ICP is limited.
- Side effects of medication:
 - Constipation
 - Abdominal discomfort
 - Malabsorption of fat and fat soluble vitamins especially at doses >4 grams per day
- Administration begins with 2 to 4 grams per day in divided doses, gradually increasing to a maximum daily dose of 16 grams as needed for symptom relief [\[59\]](#).

Cholestyramine





ICP Treatment if UDCA Alone is Ineffective

Rifampin

- Strong agonist of the pregnane X receptor (PXR), which mediates many detoxification and hepatobiliary processes.
- Relieves pruritus in nonpregnant patients when pruritis is associated with cholestasis.



Click through the screens for more details on Rifampin

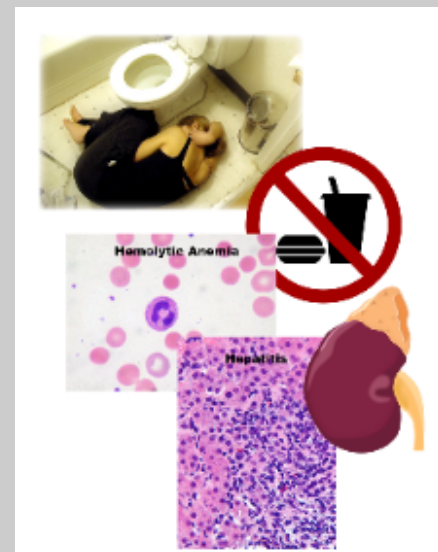
1 of 3 >



ICP Treatment if UDCA Alone is Ineffective

Medication side effects include:

- Nausea
- Decreased appetite
- Hemolytic anemia
- Renal failure
- Hepatitis



Click through the screens for more details on Rifampin

2 of 3 >



ICP Treatment if UDCA Alone is Ineffective

A total daily dose range from 300 to 1200mg orally administered in divided doses has been demonstrated to improve pruritis.



Click through the screens for more details on Rifampin

3 of 3



To move on with the lesson, use the arrows below.





ICP Treatment if UDCA Alone is Ineffective

Hydroxyzine

25mg orally every 6 to 8 hours can help with pruritis.



Click through the screens for more details on other treatments

1 of 4



Hydrazine and Chlorpheniramine





ICP Treatment if UDCA Alone is Ineffective

Chlorpheniramine

Oral administration at 4mg every 4 to 6 hours to treat pruritus with minimal efficacy, but causes sedation for sleep.



Click through the screens for more details on other treatments

2 of 4





ICP Treatment if UDCA Alone is Ineffective

Calamine lotion or aqueous cream with 2% menthol may be used for pruritus.



Click through the screens for more details on other treatments

3 of 4



Hydrazine and Chlorpheniramine





ICP Treatment if UDCA Alone is Ineffective

Dexamethasone 12mg per day did not relieve pruritus or improve serum aminotransferase levels in 130 women of a randomized trial, and was less effective than UDCA 1000mg/day at reducing bile acids and bilirubin [\[62\]](#).

Phenobarbital, charcoal, ultraviolet light, and herbal remedies have been used with uncertain efficacy.



Click through the screens for more details on other treatments

4 of 4



To move on with the lesson, use the arrows below.

Hydrazine and Chlorpheniramine



ICP Pregnancy Management - Antepartum

- There is no proven efficacy of antepartum fetal testing to reduce the risk of stillbirth; however, it is still typically performed.
- It is hypothesized that antepartum fetal testing is not useful because the mechanism of stillbirth is thought to be sudden event rather than a chronic placental vascular process.
- Antepartum fetal testing should be initiated at a gestational age at which delivery would be performed in response to abnormal fetal testing results.
- The optimal mode of testing or frequency of testing is unknown [[1](#), [67](#), [68](#)].



Click through the screens for more information.

1 of 2 >



ICP Pregnancy Management - Antepartum

Either non-stress tests (NSTs) or biophysical profiles can be performed [\[63\]](#). Other studies reported intrauterine fetal demise occurred within a few days of a reactive NST [\[64-70\]](#).



Click through the screens for more information.

2 of 2



To move on with the lesson, use the arrows below.





ICP Timing of Delivery

The timing of delivery should be individualized based on patient-specific factors including total bile acid levels:

- If total bile acids are >100 $\mu\text{mol/L}$, delivery is recommended at 36 weeks
- If total bile acids are <100 $\mu\text{mol/L}$, delivery is recommended at 36-37 weeks
- Recent data suggests that delivery can even be further delayed if bile acids are <40 $\mu\text{mol/L}$



Click through the screens for more information.

1 of 2





ICP Timing of Delivery

Delivery should be considered prior to 36 weeks in women with ICP, total bile acids >100 $\mu\text{mol/L}$ and any of the following:

- Excruciating and unremitting maternal pruritis
- History of stillbirth prior to 36 weeks due to ICP
- Pre-existing or acute hepatic disease with worsening hepatic function [[44](#), [71](#)].



Click through the screens for more information.

2 of 2



Use the arrows below to move forward with the lesson.



ICP Pregnancy Management



Counseling prior to a preterm delivery:

- All women who electively deliver prior to 36 weeks should be counseled about absence of definitive evidence that the maternal and fetal benefits of delivery outweigh the potential morbidity of prematurity.
- If preterm delivery is planned, the woman should receive a course of antenatal corticosteroids prior to delivery.



ICP Guidelines from Professional Organizations

The American College of Obstetricians and Gynecologists (ACOG)

Recommends delivery at 36+0 to 37+0 weeks of gestation or at diagnosis if diagnosed at term [\[77\]](#).

The Royal College of Obstetricians and Gynecologists (RCOG)

Recommends offering women induction of labor after 37+0 week of gestation, especially those with severe laboratory abnormalities [\[74\]](#).

1 of 2 ➡



ICP Guidelines from Professional Organizations

The Society for Maternal-Fetal Medicine(SMFM) has made recommendations for delivery based upon bile acid levels [75]:

- Bile acids under 40: delivery is recommended at 36 0/7-39 0/7 weeks gestation.
- Bile acids 40-99: delivery is recommended at 36 0/7-39 0/7 weeks gestation with a recommendation for delivery in the earlier portion of this window. For these pregnancies, delivery timing will be similar to ACOG recommendations.
- Bile acids over 100: Delivery is recommended at 36 0/7 weeks gestation. There is recommendation for delivery between 34-36 weeks gestation in these pregnancies with unrelieved itching, a prior stillbirth or worsening liver disease.
- SMFM acknowledges that delivery planning should be an individualized decision.

[Healthcare provider microlearning video](https://youtu.be/cYhexEvcJeo)

<https://youtu.be/cYhexEvcJeo>

2 of 2



ICP Delivery Recommendations



- No specific or special recommendations are considered related to delivery in a woman with ICP.
- During labor, continuous fetal monitoring is indicated related to increased occurrence of fetal death and non-fatal asphyxia events [[76](#), [78](#)].
- Increased cesarean delivery rates are not noted with induction of labor compared with expectant management.

ICP Postpartum Maternal Management

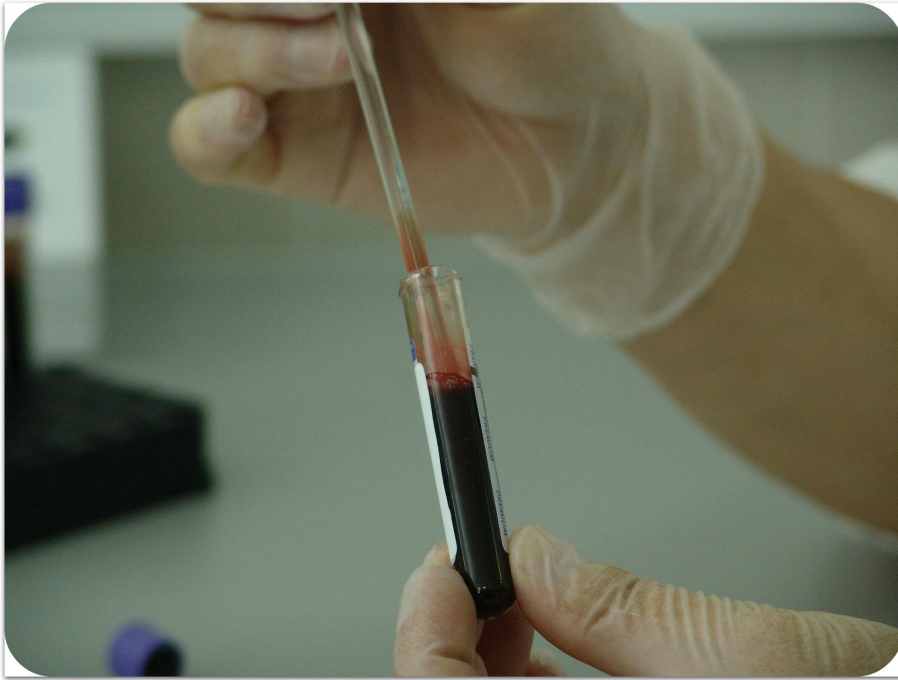


Postpartum Maternal Management

- Pruritus generally resolves in a few days following delivery.
- Serum bile acid concentrations and liver function tests are normalized in the first few days following delivery.
- Women with ICP can breastfeed without complications. UDCA is noted in low levels in breast milk; therefore, small amounts will be ingested by the infant but not expected to cause adverse effects in the infant [[79](#)].



ICP Postpartum Monitoring



Six to eight weeks following delivery, total bile acid concentration and transaminases are rechecked.

If either blood test does not return to normal, referral to a hepatologist is recommended to evaluate for hepatobiliary diseases.



ICP Postpartum Contraception



- Nonhormonal contraception may be used without complications.
- If a woman had a history of cholestasis related to use of estrogen-progestin contraception then non-estrogen contraception is preferred.
- Combination contraception, estrogen-progestin methods, rarely is associated with recurrent cholestasis.
- Centers for Disease Control and Prevention (CDC) considers estrogen-progestin contraception an acceptable choice for women with a history of ICP since the benefits outweigh the risks [\[82\]](#).
- Estrogen-progestin contraception may be initiated after liver function tests (LFT) are evaluated and normal.
 - LFT should be rechecked 3 to 6 months after initiation of estrogen-progestin contraception.
- A woman who has had ICP and uses estrogen-progestin contraception should be educated to promptly discontinue use if she develops pruritus or cholestasis.



ICP Planning and Prevention

ICP recurs in approximately 60 to 70% of women.

Severity of disease is variable in subsequent pregnancies compared to the first occurrence.





ICP Summary and Recommendations

- ICP is characterized with pruritus and elevated serum bile acid levels.
 - Pruritus is generalized but predominates on the palms of the hands and soles of the feet and is worse at night.
- ICP generally develops in the 2nd and/or 3rd trimester.
- ICP rapidly resolves following delivery.
- Diagnosis is based upon pruritus associated with elevated serum bile acid levels.
 - Twenty percent of cases of ICP are severe with a serum bile acids are $>40\mu\text{mole/L}$
- Pruritus can occur several weeks prior to lab abnormalities being noted.
- UDCA should not be started prior to a confirmed diagnosis.



ICP Summary and Recommendations

- The differential diagnosis of symptoms must be considered.
 - The lack of primary skin lesions in ICP helps to differentiate ICP from other skin conditions unrelated to pregnancy.
- The major complications of ICP include increased risk of intrauterine demise, meconium-stained amniotic fluid, preterm delivery, neonatal RDS due to association of bile acids entering the fetal lungs.
- Serum total bile acid level $\geq 100\mu\text{mole/L}$ is associated with higher risk for stillbirth.
 - Bile acid levels are monitored in all women with ICP.
 - Management is based upon the highest total serum bile concentration level.



ICP Summary and Recommendations

- The goal is to decrease maternal pruritis and possibly prevent fetal complications.
- Initiate treatment if pregnancy <37 weeks gestation.
- Treatment is with urosodeoxycholic acid; ursodiol or UDCA which are synthetic bile acids.
- UDCA reduces or relieves pruritis, has no known fetal toxicity, and is well tolerated by women. The optimal dose has not been determined; however, 300mg orally 2 to 3 times daily is reasonable. Discontinue medication when at the time of delivery.





ICP Summary and Recommendations

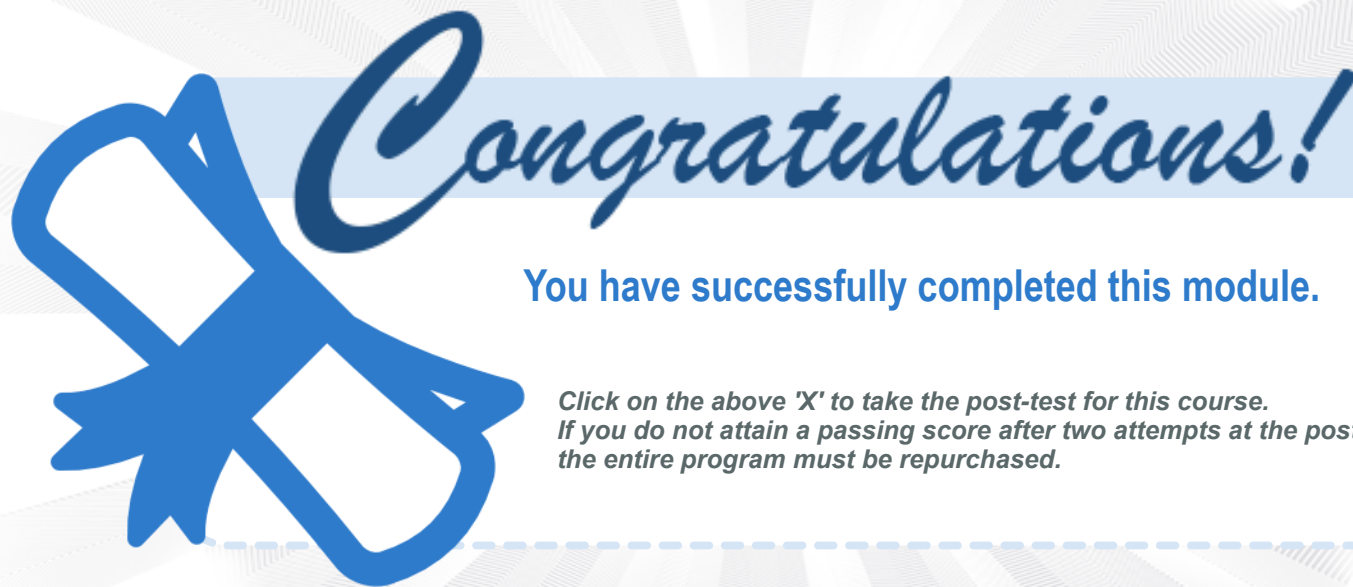
- The goal is to deliver women with ICP according to the bile acid level
 - Bile acids under 40: delivery is recommended at 36 0/7-39 0/7 weeks gestation.
 - Bile acids 40-99: delivery is recommended at 36 0/7-39 0/7 weeks gestation.
 - Bile acids over 100: is recommended at 36 0/7 weeks gestation. There is recommendation for delivery between 34-36 weeks gestation in these pregnancies with unrelieved itching, a prior stillbirth or worsening liver disease.
- Serum bile acids and liver function levels are checked six to eight weeks following delivery.
 - If recheck blood testing is not normal, referral to a hepatobiliary specialist is recommended.
- ICP recurs 60-70% of the time in subsequent pregnancies.
- Breastfeeding is considered safe when a pregnancy has been complicated with ICP.



ICP CARE

fight the itch. save a life.

To learn more about ICP, please review at <https://icpcare.org/>
Like the Facebook page <https://www.facebook.com/ICPcare>



Congratulations!

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If you do not attain a passing score after two attempts at the post-test
the entire program must be repurchased.*

1. [Clinical Updates in Women's Health Care Summary: Liver Disease: Reproductive Considerations](#). Obstet Gynecol 2017; 129:236.
2. Geenes V, Williamson C. [Intrahepatic cholestasis of pregnancy](#). World J Gastroenterol 2009; 15:2049.
3. Bacq Y. [Intrahepatic cholestasis of pregnancy](#). Clin Liver Dis 1999; 3:1.
4. Reyes H, Gonzalez MC, Ribalta J, et al. [Prevalence of intrahepatic cholestasis of pregnancy in Chile](#). Ann Intern Med 1978; 88:487.
5. Wikström Shemer E, Marschall HU, Ludvigsson JF, Stephansson O. [Intrahepatic cholestasis of pregnancy and associated adverse pregnancy and fetal outcomes: a 12-year population-based cohort study](#). BJOG 2013; 120:717.
6. Laifer SA, Stiller RJ, Siddiqui DS, et al. [Ursodeoxycholic acid for the treatment of intrahepatic cholestasis of pregnancy](#). J Matern Fetal Med 2001; 10:131.
7. Lee RH, Goodwin TM, Greenspoon J, Incerpi M. [The prevalence of intrahepatic cholestasis of pregnancy in a primarily Latina Los Angeles population](#). J Perinatol 2006; 26:527.
8. Savander M, Ropponen A, Avela K, et al. [Genetic evidence of heterogeneity in intrahepatic cholestasis of pregnancy](#). Gut 2003; 52:1025.
9. Floreani A, Gervasi MT. [New Insights on Intrahepatic Cholestasis of Pregnancy](#). Clin Liver Dis 2016; 20:177.
10. Pataia V, Dixon PH, Williamson C. [Pregnancy and bile acid disorders](#). Am J Physiol Gastrointest Liver Physiol 2017; 313:G1.
11. Jacquemin E, De Vree JM, Cresteil D, et al. [The wide spectrum of multidrug resistance 3 deficiency: from neonatal cholestasis to cirrhosis of adulthood](#). Gastroenterology 2001; 120:1448.
12. de Vree JM, Jacquemin E, Sturm E, et al. [Mutations in the MDR3 gene cause progressive familial intrahepatic cholestasis](#). Proc Natl Acad Sci U S A 1998; 95:282.
13. Jacquemin E, Cresteil D, Manouvrier S, et al. [Heterozygous non-sense mutation of the MDR3 gene in familial intrahepatic cholestasis of pregnancy](#). Lancet 1999; 353:210.
14. Dixon PH, Weerasekera N, Linton KJ, et al. [Heterozygous MDR3 missense mutation associated with intrahepatic cholestasis of pregnancy: evidence for a defect in protein trafficking](#). Hum Mol Genet 2000; 9:1209.
15. Lucena JF, Herrero JI, Quiroga J, et al. [A multidrug resistance 3 gene mutation causing cholelithiasis, cholestasis of pregnancy, and adulthood biliary cirrhosis](#). Gastroenterology 2003; 124:1037.
16. Müllenbach R, Linton KJ, Wiltshire S, et al. [ABCB4 gene sequence variation in women with intrahepatic cholestasis of pregnancy](#). J Med Genet 2003; 40:e70.

17. Pauli-Magnus C, Lang T, Meier Y, et al. Sequence analysis of bile salt export pump (ABCB11) and multidrug resistance p-glycoprotein 3 (ABCB4, MDR3) in patients with intrahepatic cholestasis of pregnancy. Pharmacogenetics 2004; 14:91.
18. Floreani A, Carderi I, Paternoster D, et al. Intrahepatic cholestasis of pregnancy: three novel MDR3 gene mutations. Aliment Pharmacol Ther 2006; 23:1649.
19. Bacq Y, Gendrot C, Perrotin F, et al. ABCB4 gene mutations and single-nucleotide polymorphisms in women with intrahepatic cholestasis of pregnancy. J Med Genet 2009; 46:711.
20. Dixon PH, Williamson C. The pathophysiology of intrahepatic cholestasis of pregnancy. Clin Res Hepatol Gastroenterol 2016; 40:141.
21. Wånggren K, Sparre LS, Wramsby H. Severe jaundice in early IVF pregnancy. Eur J Obstet Gynecol Reprod Biol 2004; 112:228.
22. Mutlu MF, Aslan K, Guler I, et al. Two cases of first onset intrahepatic cholestasis of pregnancy associated with moderate ovarian hyperstimulation syndrome after IVF treatment and review of the literature. J Obstet Gynaecol 2017; 37:547.
23. Meng LJ, Reyes H, Palma J, et al. Effects of ursodeoxycholic acid on conjugated bile acids and progesterone metabolites in serum and urine of patients with intrahepatic cholestasis of pregnancy. J Hepatol 1997; 27:1029.
24. Abu-Hayyeh S, Ovadia C, Lieu T, et al. Prognostic and mechanistic potential of progesterone sulfates in intrahepatic cholestasis of pregnancy and pruritus gravidarum. Hepatology 2016; 63:1287.
25. Bacq Y, Sapey T, Bréchet MC, et al. Intrahepatic cholestasis of pregnancy: a French prospective study. Hepatology 1997; 26:358.
26. Pařízek A, Dušková M, Vítek L, et al. The role of steroid hormones in the development of intrahepatic cholestasis of pregnancy. Physiol Res 2015; 64 Suppl 2:S203.
27. Marschall HU, Wikström Shemer E, Ludvigsson JF, Stephansson O. Intrahepatic cholestasis of pregnancy and associated hepatobiliary disease: a population-based cohort study. Hepatology 2013; 58:1385.
28. Ropponen A, Sund R, Riikonen S, et al. Intrahepatic cholestasis of pregnancy as an indicator of liver and biliary diseases: a population-based study. Hepatology 2006; 43:723.
29. Leevy CB, Koneru B, Klein KM. Recurrent familial prolonged intrahepatic cholestasis of pregnancy associated with chronic liver disease. Gastroenterology 1997; 113:966.
30. Turunen K, Mölsä A, Helander K, et al. Health history after intrahepatic cholestasis of pregnancy. Acta Obstet Gynecol Scand 2012; 91:679.

31. Hubschmann AG, Orzechowski KM, Berghella V. Severe First Trimester Recurrent Intrahepatic Cholestasis of Pregnancy: A Case Report and Literature Review. AJP Rep 2016; 6:e38.
32. Kondrackiene J, Kupcinskas L. Intrahepatic cholestasis of pregnancy-current achievements and unsolved problems. World J Gastroenterol 2008; 14:5781.
33. Heikkinen J, Mäentausta O, Ylöstalo P, Jänne O. Changes in serum bile acid concentrations during normal pregnancy, in patients with intrahepatic cholestasis of pregnancy and in pregnant women with itching. Br J Obstet Gynaecol 1981; 88:240.
34. Lunzer M, Barnes P, Byth K, O'Halloran M. Serum bile acid concentrations during pregnancy and their relationship to obstetric cholestasis. Gastroenterology 1986; 91:825.
35. Kenyon AP, Piercy CN, Girling J, et al. Obstetric cholestasis, outcome with active management: a series of 70 cases. BJOG 2002; 109:282.
36. Brites D, Rodrigues CM, Oliveira N, et al. Correction of maternal serum bile acid profile during ursodeoxycholic acid therapy in cholestasis of pregnancy. J Hepatol 1998; 28:91.
37. Diken Z, Usta IM, Nassar AH. A clinical approach to intrahepatic cholestasis of pregnancy. Am J Perinatol 2014; 31:1.
38. Huang WM, Gowda M, Donnelly JG. Bile acid ratio in diagnosis of intrahepatic cholestasis of pregnancy. Am J Perinatol 2009; 26:291.
39. Manzotti C, Casazza G, Stimac T, et al. Total serum bile acids or serum bile acid profile, or both, for the diagnosis of intrahepatic cholestasis of pregnancy (Protocol). Cochrane Database Syst Rev 2017; :CD012546.
40. Engelking LR, Dasher CA, Hirschowitz BI. Within-day fluctuations in serum bile-acid concentrations among normal control subjects and patients with hepatic disease. Am J Clin Pathol 1980; 73:196.
41. Vanjak D, Moreau R, Roche-Sicot J, et al. Intrahepatic cholestasis of pregnancy and acute fatty liver of pregnancy. An unusual but favorable association? Gastroenterology 1991; 100:1123.
42. Rioseco AJ, Ivankovic MB, Manzur A, et al. Intrahepatic cholestasis of pregnancy: a retrospective case-control study of perinatal outcome. Am J Obstet Gynecol 1994; 170:890.
43. Geenes V, Lövgren-Sandblom A, Benthin L, et al. The reversed feto-maternal bile acid gradient in intrahepatic cholestasis of pregnancy is corrected by ursodeoxycholic acid. PLoS One 2014; 9:e83828.
44. Ovadia C, Seed PT, Sklavounos A, et al. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers:

results of aggregate and individual patient data meta-analyses. Lancet 2019; 393:899.

45. Williamson C, Miragoli M, Sheikh Abdul Kadir S, et al. Bile acid signaling in fetal tissues: implications for intrahepatic cholestasis of pregnancy. Dig Dis 2011; 29:58.
46. Sepúlveda WH, González C, Cruz MA, Rudolph MI. Vasoconstrictive effect of bile acids on isolated human placental chorionic veins. Eur J Obstet Gynecol Reprod Biol 1991; 42:211.
47. Geenes V, Chappell LC, Seed PT, et al. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population-based case-control study. Hepatology 2014; 59:1482.
48. Williamson C, Hems LM, Goulis DG, et al. Clinical outcome in a series of cases of obstetric cholestasis identified via a patient support group. BJOG 2004; 111:676.
49. Germain AM, Kato S, Carvajal JA, et al. Bile acids increase response and expression of human myometrial oxytocin receptor. Am J Obstet Gynecol 2003; 189:577.
50. Israel EJ, Guzman ML, Campos GA. Maximal response to oxytocin of the isolated myometrium from pregnant patients with intrahepatic cholestasis. Acta Obstet Gynecol Scand 1986; 65:581.
51. Kremer AE, Oude Elferink RP, Beuers U. Pathophysiology and current management of pruritus in liver disease. Clin Res Hepatol Gastroenterol 2011; 35:89.
52. Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. Obstet Gynecol 2014; 124:120.
53. Pusi T, Beuers U. Intrahepatic cholestasis of pregnancy. Orphanet J Rare Dis 2007; 2:26.
54. Bacq Y, le Besco M, Lecuyer AI, et al. Ursodeoxycholic acid therapy in intrahepatic cholestasis of pregnancy: Results in real-world conditions and factors predictive of response to treatment. Dig Liver Dis 2017; 49:63.
55. Mazzella G, Rizzo N, Azzaroli F, et al. Ursodeoxycholic acid administration in patients with cholestasis of pregnancy: effects on primary bile acids in babies and mothers. Hepatology 2001; 33:504.
56. Ozkan S, Ceylan Y, Ozkan OV, Yildirim S. Review of a challenging clinical issue: Intrahepatic cholestasis of pregnancy. World J Gastroenterol 2015; 21:7134.
57. Zhang Y, Lu L, Victor DW, et al. Ursodeoxycholic Acid and S-adenosylmethionine for the Treatment of Intrahepatic Cholestasis of Pregnancy: A Meta-analysis. Hepat Mon 2016; 16:e38558.

58. Coltorti M, Bortolini M, Di Padova C. A review of the studies on the clinical use of S-adenosylmethionine (SAME) for the symptomatic treatment of intrahepatic cholestasis. Methods Find Exp Clin Pharmacol 1990; 12:69.
59. Mela M, Mancuso A, Burroughs AK. Review article: pruritus in cholestatic and other liver diseases. Aliment Pharmacol Ther 2003; 17:857.
60. Liu J, Murray AM, Mankus EB, et al. Adjuvant Use of Rifampin for Refractory Intrahepatic Cholestasis of Pregnancy. Obstet Gynecol 2018; 132:678.
61. Geenes V, Chambers J, Khurana R, et al. Rifampicin in the treatment of severe intrahepatic cholestasis of pregnancy. Eur J Obstet Gynecol Reprod Biol 2015; 189:59.
62. Glantz A, Marschall HU, Lammert F, Mattsson LA. Intrahepatic cholestasis of pregnancy: a randomized controlled trial comparing dexamethasone and ursodeoxycholic acid. Hepatology 2005; 42:1399.
63. Fisk NM, Storey GN. Fetal outcome in obstetric cholestasis. Br J Obstet Gynaecol 1988; 95:1137.
64. Alsulyman OM, Ouzounian JG, Ames-Castro M, Goodwin TM. Intrahepatic cholestasis of pregnancy: perinatal outcome associated with expectant management. Am J Obstet Gynecol 1996; 175:957.
65. Laatikainen T, Tulenheimo A. Maternal serum bile acid levels and fetal distress in cholestasis of pregnancy. Int J Gynaecol Obstet 1984; 22:91.
66. Sentilhes L, Verspyck E, Pia P, Marpeau L. Fetal death in a patient with intrahepatic cholestasis of pregnancy. Obstet Gynecol 2006; 107:458.
67. Lee RH, Incerpi MH, Miller DA, et al. Sudden fetal death in intrahepatic cholestasis of pregnancy. Obstet Gynecol 2009; 113:528.
68. Laatikainen T. Effect of cholestyramine and phenobarbital on pruritus and serum bile acid levels in cholestasis of pregnancy. Am J Obstet Gynecol 1978; 132:501.
69. Saleh MM, Abdo KR. Consensus on the management of obstetric cholestasis: National UK survey. BJOG 2007; 114:99.
70. Matos A, Bernardes J, Ayres-de-Campos D, Patrício B. Antepartum fetal cerebral hemorrhage not predicted by current surveillance methods in cholestasis of pregnancy. Obstet Gynecol 1997; 89:803.
71. Brouwers L, Koster MP, Page-Christiaens GC, et al. Intrahepatic cholestasis of pregnancy: maternal and fetal outcomes associated with elevated bile acid levels. Am J Obstet Gynecol 2015; 212:100.e1.
72. Rook M, Vargas J, Caughey A, et al. Fetal outcomes in pregnancies complicated by intrahepatic cholestasis of pregnancy in a Northern California cohort. PLoS One 2012; 7:e28343.

73. Eggerman RS, Riely CA. Predicting fetal outcome in intrahepatic cholestasis of pregnancy: is the bile acid level sufficient? Hepatology 2004; 40:287
74. Obstetric Cholestasis (Green-top Guideline No. 43)
<https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg43/>.
75. Society for Maternal-Fetal Medicine (SMFM). Electronic address: pubs@smfm.org, Lee RH, Mara Greenberg, Metz TD, Pettker CM. Society for Maternal-Fetal Medicine Consult Series #53: Intrahepatic cholestasis of pregnancy: Replaces Consult #13, April 2011. Am J Obstet Gynecol. 2020 Nov 13:S0002-9378(20)31284-9. doi: 10.1016/j.ajog.2020.11.002. Epub ahead of print. PMID: 33197417.
76. American College of Obstetricians and Gynecologists. ACOG committee opinion no. 764: Medically indicated Late-Preterm and Early-Term Deliveries. Obstet Gynecol 2019.
77. Oztekin D, Aydal I, Oztekin O, et al. Predicting fetal asphyxia in intrahepatic cholestasis of pregnancy. Arch Gynecol Obstet 2009; 280:975.
78. Maldonado M, Alhousseini A, Awadalla M, et al. Intrahepatic Cholestasis of Pregnancy Leading to Severe Vitamin K Deficiency and Coagulopathy. Case Rep Obstet Gynecol 2017; 2017:5646247.
79. Hirvioja ML, Kivinen S. Inheritance of intrahepatic cholestasis of pregnancy in one kindred. Clin Genet 1993; 43:315.
80. Bicocca MJ, Sperling JD, Chauhan SP. Intrahepatic cholestasis of pregnancy: Review of six national and regional guidelines. Eur J Obstet Gynecol Reprod Biol 2018; 231:180.
81. Kenyon AP, Tribe RM, Nelson-Piercy C, et al. Pruritus in pregnancy: a study of anatomical distribution and prevalence in relation to the development of obstetric cholestasis. Obstet Med 2010; 3:25.
82. Tran, TT, Ahn, J, Reau, NS. ACG Clinical Guideline: Liver Disease and Pregnancy. Am J Gastroenterol 2016; 111:176-194; doi:10.1038/ajg.2015.430
83. Zecca E, De Luca D, Baroni S, et al. Bile acid-induced lung injury in newborn infants: a bronchoalveolar lavage fluid study. Pediatrics 2008; 121:e146.
84. Grand'Maison, S, Durand, M, Mahone, M. The effects of ursodeoxycholic acid treatment for intrahepatic cholestasis of pregnancy on maternal and fetal outcomes: A meta-analysis including non-randomized studies. J Obstet Gynaecol Can 2014; 36(7):632-641.
85. Cui, D, Zhong, Y, Zhang, L, Du, H. Bile acid levels and risk of adverse perinatal outcomes in intrahepatic cholestasis of pregnancy: A meta-analysis. J. Obstet. Gynaecol. Res. Vol. 43, No. 9: 1411-1420; September 2017. Doi:10.1111/jog.13399

86. Wikström Shemer EA, Stephansson O, Thuresson M, et al. Intrahepatic cholestasis of pregnancy and cancer, immune-mediated and cardiovascular diseases: A population-based cohort study. J Hepatol 2015; 63:456.
87. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. MMWR Recomm Rep 2016; 65:1.