



## 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





**The course will:**

- Help participants develop sound clinical judgment in the delivery of health care in a labor and delivery unit and postpartum 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 delivery in a labor and delivery unit 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.



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- Planning and Prevention
- Summary and Recommendations





Meet Tamara, Ken, Juanita and Michael.

- Tamara will take you through the basics.
- Ken will take you through the patient presentation and physical exam.
- Juanita will take you through diagnosing ICP.
- Michael will take you through patient management.

## Intrahepatic Cholestasis of Pregnancy (ICP) Definition

Women who present with ICP have pruritus and elevation in serum bile acid concentrations. This condition generally develops in the late second and/or third trimester of pregnancy.



**ICP rapidly resolves following delivery.**



# ICP Incidence Rate and Epidemiology



**ICP is the most common liver disease exclusive to pregnancy [1].**

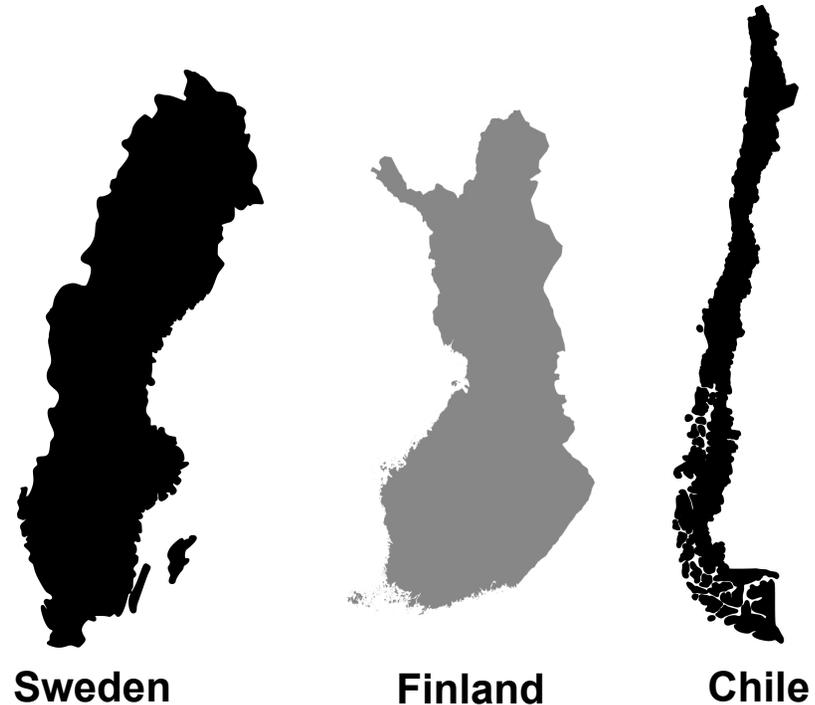
The incidence rate varies worldwide, from <1 to 27.6%. There are no known reasons for the variance in rates [2, 3]. It is thought the differences among population groups and environmental factors may contribute to the incident rates [4, 5].

# ICP Incidence Rate and Epidemiology

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

In a study performed in Chile, ICP occurred at a higher rate in multiple gestations; in twins 20.9% were affected while in single gestation 4.7% were affected [9].

In a Finland study, ICP occurred in 43% of triplet pregnancies versus 14% of twin pregnancies [10].

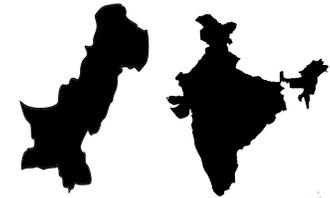


Finland - Single Color by FreeVectorMaps.com

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



**This rate is followed by the Indian-Asians and Pakistani Asians, with an incident rate of 1.2 to 1.5% [8].**



**In Europe, 0.5 to 1.5% of Scandinavia women are affected [2].**

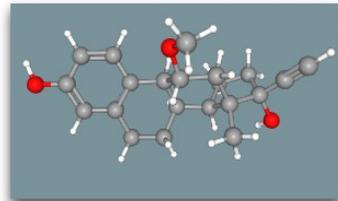


**In the United States, the occurrence rate is from 0.32% of women in Bridgeport Hospital, Connecticut to 5.6% in a Hispanic population in Los Angeles, California [6, 7].**





**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](#)

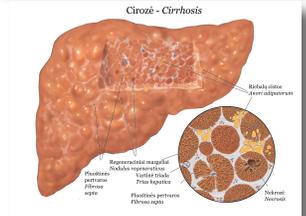


**Other factors that affect the incident rate include: [11]**

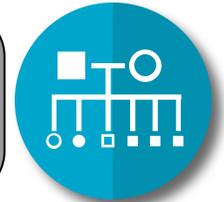
**Personal history of chronic hepatitis C**



**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

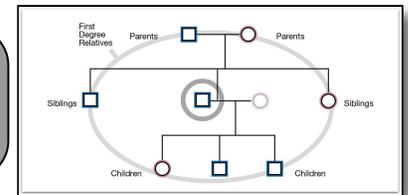


The genetic cause of ICP is very complicated, but genetic susceptibility in evidence demonstrates [12]:

**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 adenosine triphosphate-binding cassette, subfamily B, member 4 (ABCB4) gene encoding the multidrug resistance 3 (MDR3) protein [13].

- 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 [16-21].
- In a consanguineous family, a woman having ICP is more likely to have a heterozygous mutation in ABCB4 (also called MDR3) [14, 15].
- Other genes possibly involved in ICP pathogenesis include ABCB11, ATP8B1, ABCC2, NR1H4) [16, 17, 18, 19, 20, 21, 22, 23].



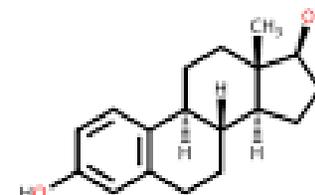
# Etiology - Hormone Effect in ICP

## Estrogen [9, 27, 28]

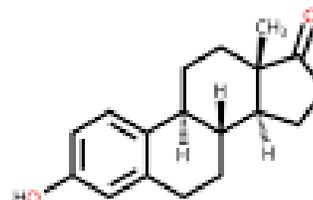
In experimental and clinical studies, estrogen has been associated with ICP.

- 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 at higher rates in multiple gestation.

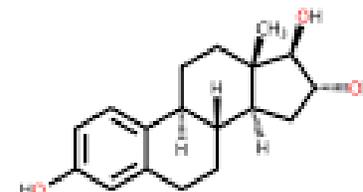
### ESTROGENS



Estradiol



Estrone



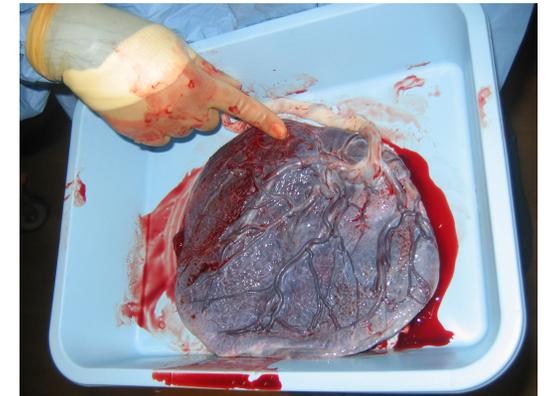
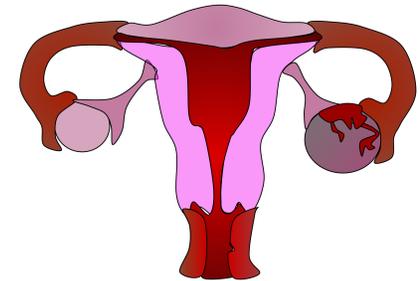
Estriol

# 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, so ICP resolves after delivery of the placenta.



# Etiology - Hormone Effect in ICP

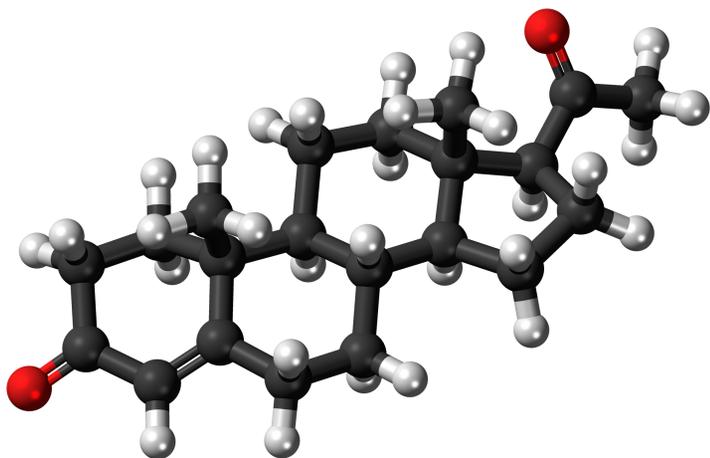


**Progesterone metabolism may contribute to the pathogenesis of ICP.**

## Progesterone

- In women who are genetically predisposed, the development of large amounts of sulfated progesterone metabolites in pregnancy and may result in saturation of the hepatic transport system used for biliary excretion of these compounds [[29](#), [30](#)]. This may be associated with greater 5-alpha and 3-alpha reduction [[29](#), [30](#)].
- Sulfotransferase activity is decreased in pregnancy [[31](#)].

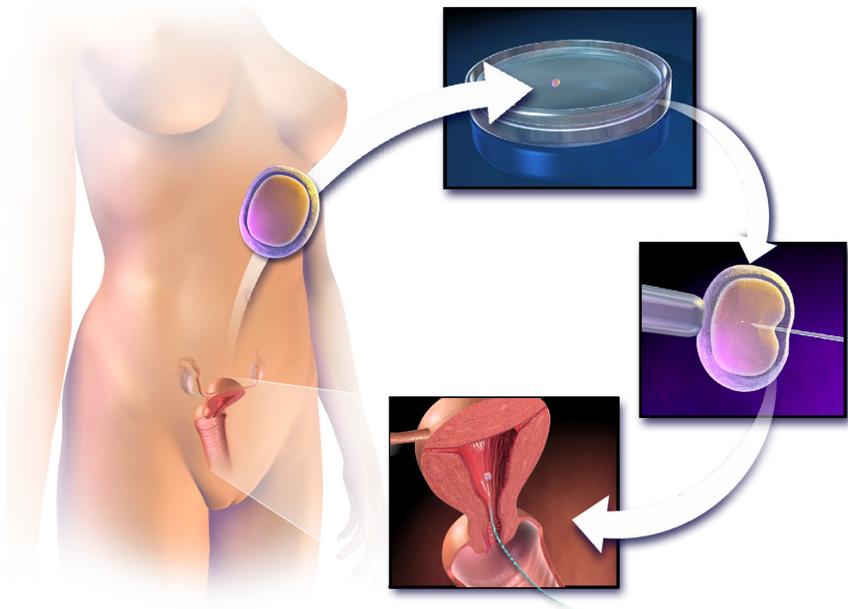
## Etiology - Hormone Effect in ICP



**Progesterone molecule**

- 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. In addition, the package insert indicates contraindications to use of Makena, including an 8% increase of pruritis in users. In addition, package insert indicates contraindications to use Makena include cholestatic jaundice of pregnancy, benign or malignant liver tumors, or active liver disease [32].

# 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. Data on occurrence rates is limited to case reports [27].

## Etiology - Special Populations and Hormone Effects



**Deciding to initiate progesterone supplementation should be discussed with the woman.**

**The discussion should include risks and benefits.**

- It is uncertain if providing progesterone supplementation to women with a history of previous preterm birth (PTB) or a short cervical length in the current pregnancy should be avoided if she has a previous history of ICP.
- Progesterone supplementation risks include a PTB in the current pregnancy, the gestational age of a recurrent preterm birth with or without progesterone supplement, and the risk and possible ramification of recurrent ICP.
- If progesterone supplementation is initiated and she develops ICP, it is recommended the medication be discontinued.

# Etiology- Environmental Factors in ICP

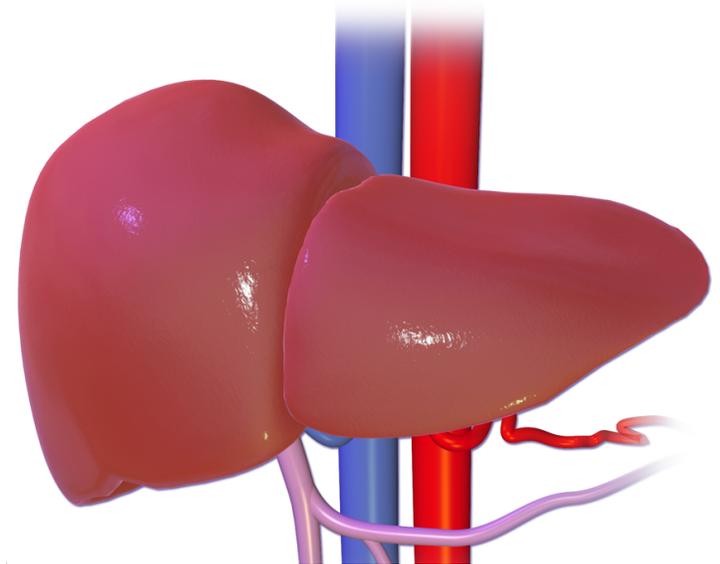


**Environmental factors affect the expression of ICP.**

- Seasonal and geographic variables influence the expression of this disease.
- Definite aspects in the environment have not been identified. 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 [34-37].
- Hepatitis C and nonalcoholic liver cirrhosis were associated with ICP in a large population-based study [35].
- In another review, 4 sisters had an atypical familial form of prolonged recurrent ICP during pregnancy and developed progressive fibrosis [36].



# ICP Patient 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.**

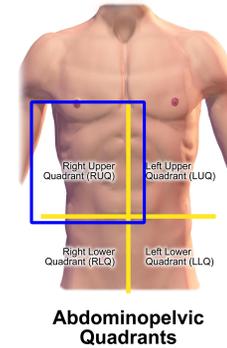
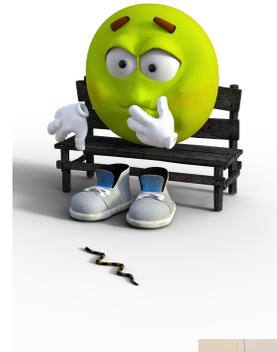
**Pruritis is usually worse at night.**

# ICP Patient Presentation



**Other ICP symptoms that may occur include:**

**Click on the pictures for the symptoms of ICP.**



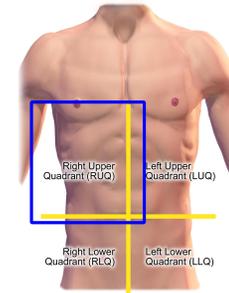
# ICP Patient Presentation



Other ICP symptoms that may occur include:

Click on the pictures for the symptoms of ICP.

Nausea



Right Upper Quadrant Pain

Abdominopelvic Quadrants

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 [28].
- Symptoms that are persistent and worsening occur in women who have naturally conceived [38].
- 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 pruritis may present with scratch marks and excoriations.

Prurigo nodules may occur secondary to scratching. No primary skin lesions are associated with ICP.



Click on the picture for a larger view.





# ICP Physical Examination



**In women with ICP, 14 to 25% will develop jaundice. Jaundice generally develops one to four weeks after the itching begins [39].**

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



**Click on the picture for a larger view.**



# 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 [108].



Click the silhouette for more information.



Over 90% of affected women will have an increase in total serum bile acid (TSBA) concentration. This is the key laboratory finding in ICP. Increased TSBA may be the only laboratory abnormality [32, 40, 41].

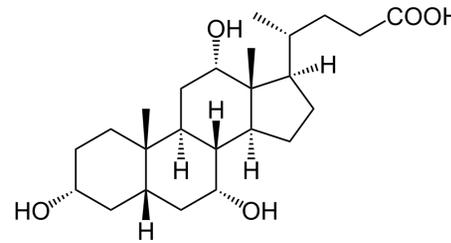
Pruritus may occur prior to laboratory abnormalities [42].



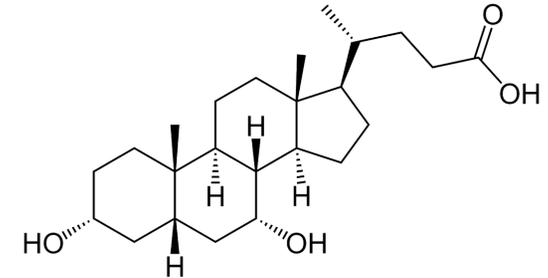
# ICP Laboratory Findings



The normal physiological changes that occur in pregnancy must be considered when performing a workup of abnormal liver tests in a pregnant woman [108].



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 [39, 44, 45]. A ratio of these two acids is not necessary to diagnose ICP [46].

## Other possible laboratory findings include:



Click the rectangles to reveal.

Serum aminotransferases (AST) increases in 60% of cases. This increase is 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].

Alkaline phosphatase may increase four times the normal value but is not specific for ICP as this may be elevated due to placental isoenzyme.

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) 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.

Prothrombin time (PT) is usually normal with ICP. When PT is protracted, it is usually secondary to vitamin K deficiency from fat malabsorption due to severe steatorrhea or secondary to use of bile acid sequestrants, instead of liver dysfunction [43].



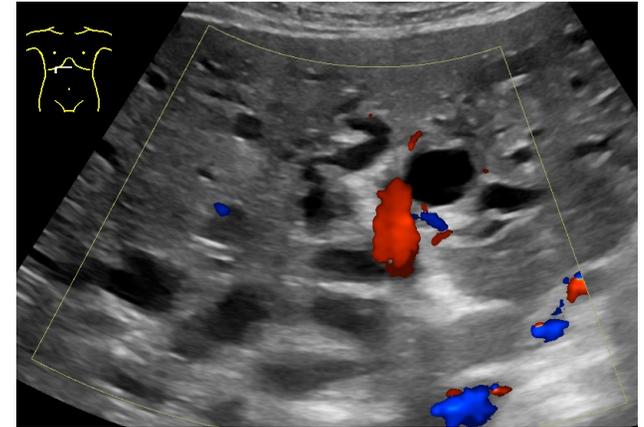
# Ultrasonography



**Ultrasonography is not necessary in diagnosing ICP.**

Women with ICP do not have abnormal findings on ultrasound.

- Biliary ducts are not dilated.
- Hepatic parenchyma appears normal.

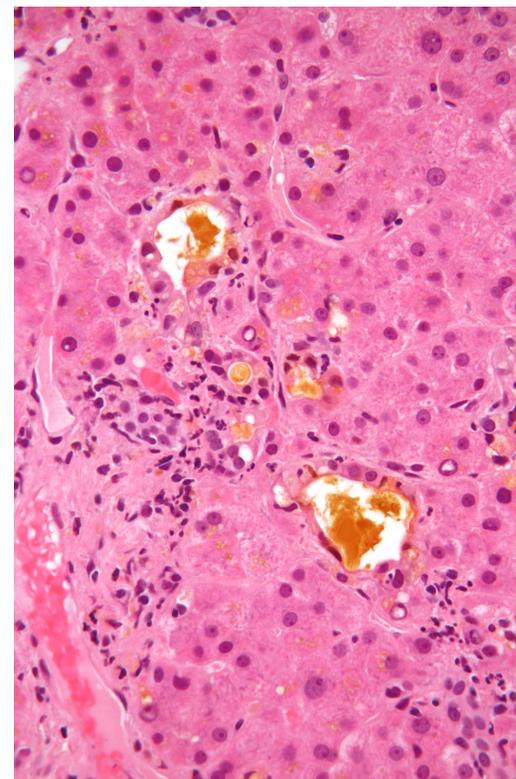


Ultrasound of dilated bile ducts

# ICP Pathology



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

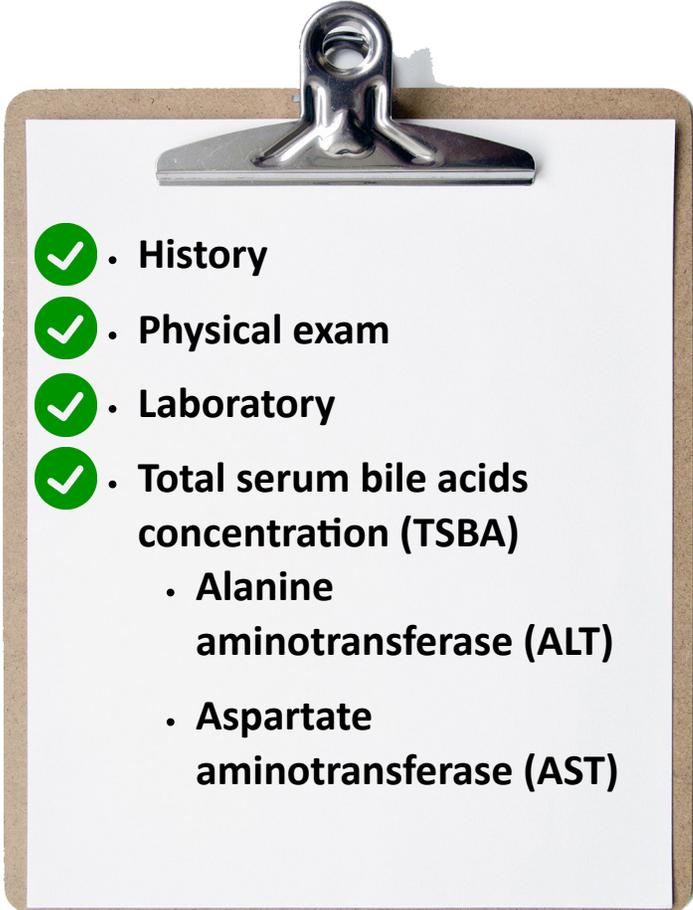


Cholestasis 2 - High Magnification

# Differential Diagnosis



To rule in a diagnosis of ICP the following must be evaluated:

- 
- ✓ . History
  - ✓ . Physical exam
  - ✓ . Laboratory
  - ✓ . Total serum bile acids concentration (TSBA)
    - . Alanine aminotransferase (ALT)
    - . Aspartate aminotransferase (AST)

# Differential Diagnosis



**Pruritus and hepatic dysfunction possible causes:**

- Pruritus gravidarum
- Atopic eruption of pregnancy
- Polymorphic eruption of pregnancy
- Pemphigoid gestationis
- Prurigo of pregnancy
- Pruritic folliculitis of pregnancy



# Differential Diagnosis



Evaluate preexisting causes of pruritus:

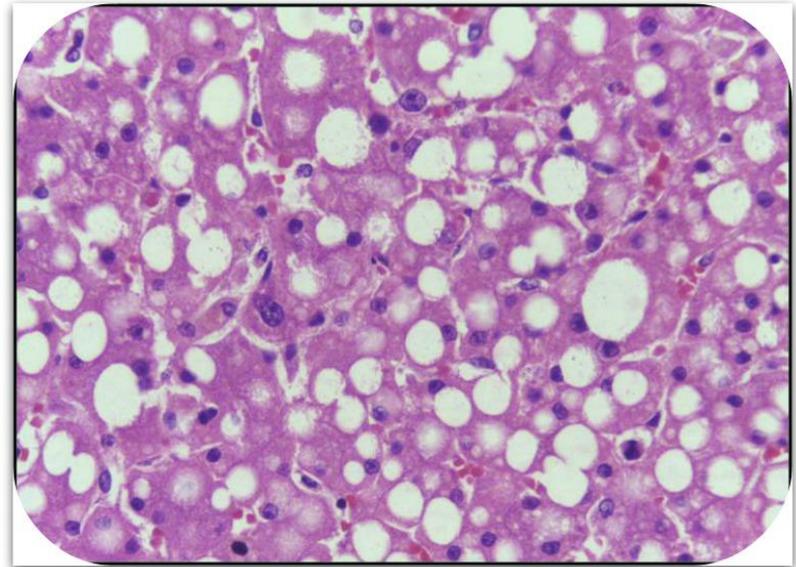


- Atopic dermatitis (shown above)
- Allergic or drug reaction
- Systemic disease

# Differential Diagnosis



**Here are some pregnancy specific causes of hepatic impairment:**

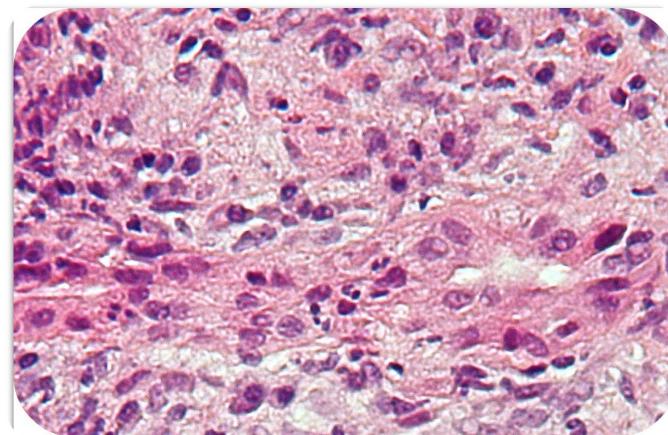


- Acute fatty liver of pregnancy (shown above)
- Hemolysis, elevated liver enzymes and low platelets syndrome (HELLP)
- Hyperemesis gravidarum

# Differential Diagnosis



**Here are some preexisting causes of hepatic impairment:**



- Primary biliary cirrhosis (shown above) or primary sclerosing cholangitis
- Viral hepatitis
- Autoimmune hepatitis
- Drug-induced liver injury
- Biliary obstruction
- Venocclusive disease

# Differential Diagnosis



**Pruritus occurs in 23% of pregnancies [52].**

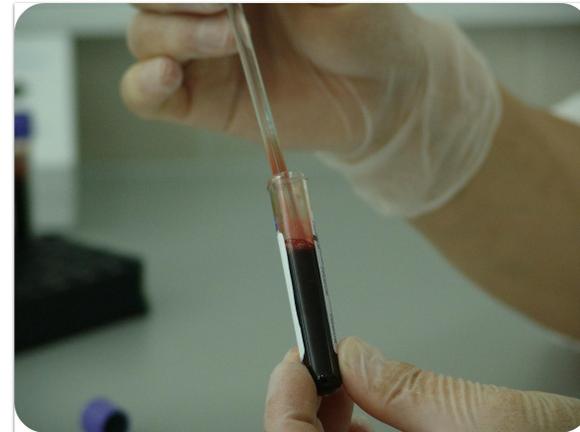


- Pruritus is the cardinal sign of ICP which does not support:
  - HELLP syndrome
  - Preeclampsia with severe features
  - Acute fatty liver of pregnancy
- ICP can however be associated with development of preeclampsia [53,54,55] and acute fatty liver of pregnancy [56].
- ICP does not present with primary skin lesions and helps distinguish it from:
  - Pregnancy-specific pruritic dermatoses
  - Skin conditions unrelated to pregnancy

# ICP Diagnosis



Here are some items to consider in diagnosing ICP:



Diagnosis is based upon [\[109\]](#):

- Pruritus
- Elevated TSBA levels
- Elevated AST
- Both elevated TSBA and AST with the absence of diseases that cause similar symptoms and laboratory results.

# ICP Diagnosis



**There are guideline variations in laboratory criteria; however, severe cholestasis is consistently defined as bile acids greater than 40µmole/L and account for nearly 20% of cases [48, 49].**

TSBA, with a cutoff level of 10µmole/L, were evaluated in a systemic review of 11 studies. The sensitivity was 0.91 and specificity was 0.93 in this review. Uncertainty remains in the accuracy of TSBA in diagnosing ICP because most studies lacked a cross-sectional design that enrolled pregnant women [49].



# ICP Diagnosis



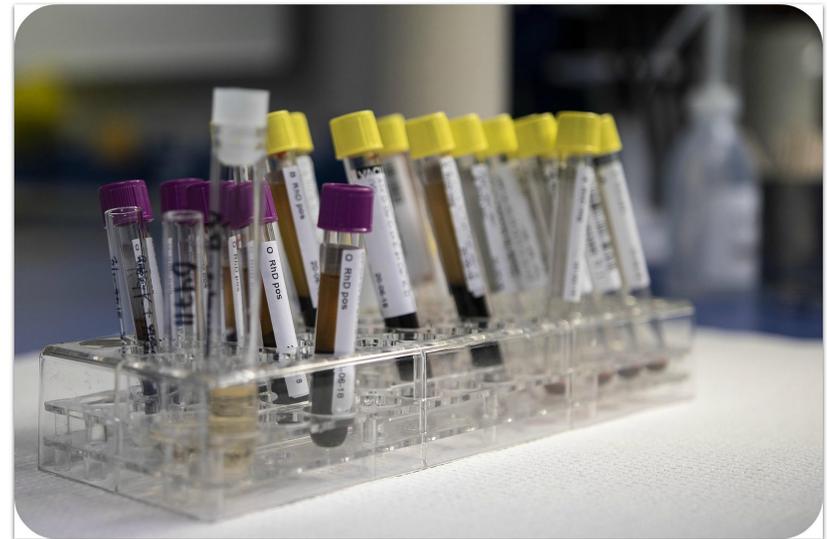
**Pregnancy does not affect AST levels.**



- Trimester specific reference ranges for 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 which are lower than when she eats, population, and trimester age [50, 51].
- 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.
- If Ursodeoxycholic acid (UCDA) is started based on pruritus, there may not be a noted increase in bile acid or AST levels.



# ICP Fetal Complications

Transplacental gradients facilitate fetal clearance of bile acids in normal pregnancies [32, 57].



## ICP Fetal Complications

Transplacental gradients facilitate fetal clearance of bile acids in normal pregnancies [32, 57].

In pregnancies affected by ICP, the transplacental gradient is reversed and an accumulation of bile acids occurs in the amniotic fluid and fetus [58].

In ICP there is increased risk for [59, 60]:

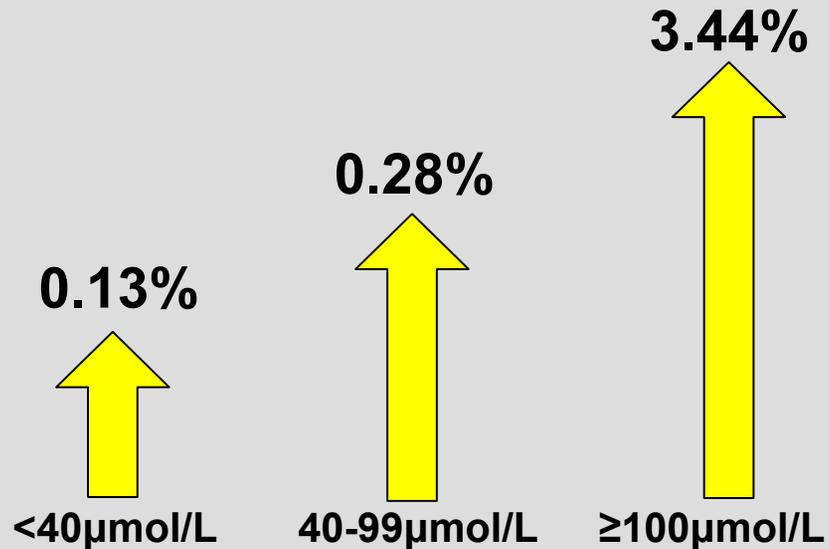
- Intrauterine fetal demise (IUFD)
- Meconium-stained amniotic fluid
- Spontaneous preterm birth
- Iatrogenic preterm birth
- Neonatal respiratory distress syndrome (RDS)
- Neonatal intensive care unit (NICU) admissions



## 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.



## ICP Fetal Complications

- The rate of stillbirth increases with increasing gestational age, especially after 34 to 36 weeks.
- The role of early delivery is a factor in statistics as demonstrated by the high iatrogenic preterm birth rate in women with ICP.

2 of 2

## 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 [61]
- Vasospasm of the placental chorionic surface vessels [62]
- Concurrent pregnancy complications such as gestational diabetes or preeclampsia [63]



## ICP Fetal Complications

Bile acids increase expression of myometrial oxytocin receptors, which is believed to be associated with spontaneous preterm labor. These pregnancies also have an earlier onset of pruritus [[64](#), [65](#), [66](#)].



2 of 3 >>



# ICP Fetal Complications

- Features not associated with ICP [32]
- Oligohydramnios
  - Fetal growth restriction



3 of 3



# ICP Maternal Treatment

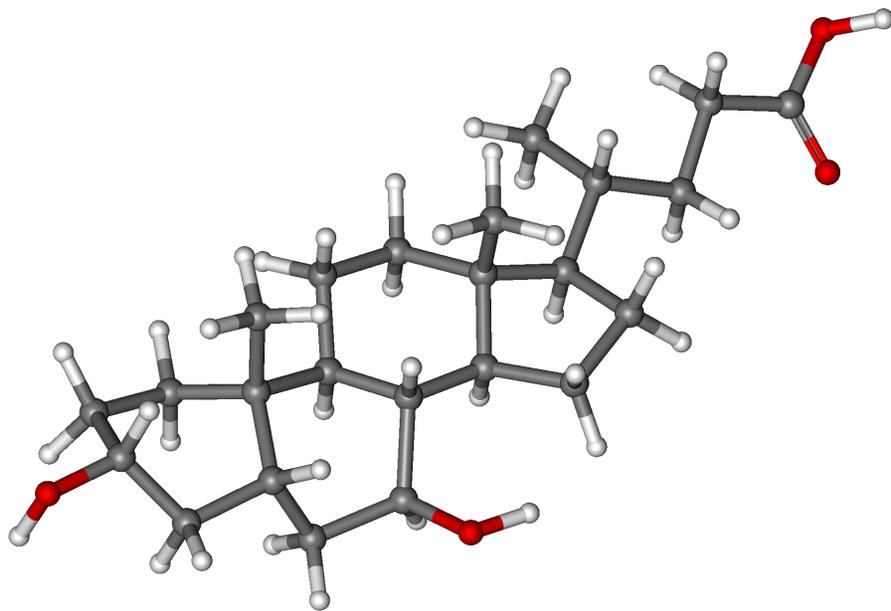


**ICP treatment focuses on pruritus.**



- Maternal treatment focuses on reducing both the pruritus she is experiencing and the risk of perinatal morbidity and mortality.
- There is no other serious maternal symptoms other than pruritus; however this can be severe.
- Women with normal serum bile acid and AST levels can be offered options:
  - Empiric treatment
  - Laboratory testing repeated weekly and treatment started when the TSBA or AST levels or both become elevated

# ICP Maternal Treatment



The preferred medication for treatment of maternal pruritus due to ICP is Ursodeoxycholic acid (UDCA) (*Shown on the left*) [67]. No additional lab testing is needed prior to initiating UDCA other than those drawn for diagnosis of ICP.

A meta-analysis in 2019 identified the efficacy of UDCA for reducing maternal symptoms and adverse perinatal outcomes [72, 73, 74].

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

# ICP Maternal Treatment



- There is no well-defined dose of UDCA but recommendations include taking until delivery [48]:
  - UDCA 300mg orally three times a day or 15mg/kg per day
  - UDCA 300mg orally twice daily or 10mg/kg per day
- If pruritus is not decreased in 2 weeks of starting UDCA, the dose is increased every 1 or 2 weeks until symptoms are relieved to a maximum dose of 21mg/kg per day [68,69,70,71].

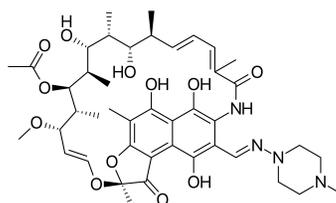
# ICP Maternal Treatment



**UDCA is tolerated well by most women; however, 25% of women may develop mild nausea and dizziness.**

- Following the initiation of UDCA, weekly maternal TSBA concentrations are monitored because significantly increased risk of stillbirth is noted when maternal concentrations  $\geq 100\mu\text{mole/L}$  [60].
- Improvement in lab results is seen in 3 to 4 weeks.
- UDCA is discontinued when labor begins if used for management of ICP symptoms.

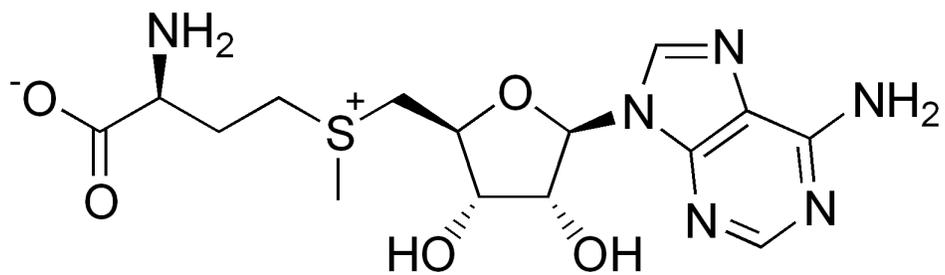
# ICP Maternal Treatment



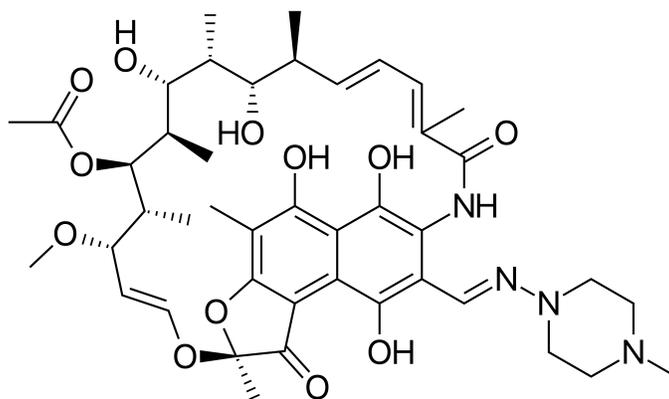
Click the chemical structure for a look at the chemical structures for each medication.

One of these drugs can be ADDED if pruritis is not relieved with UDCA:

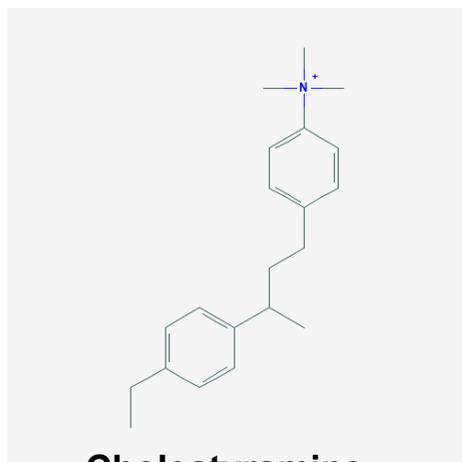
- Studies of combination use of medication for treatment of symptoms with ICP are limited to less than 30 patients [80,81].
  - S-Adenosyl-methionine (SAME)
  - Cholestyramine
  - Rifampin (aka rifampicin)
- Alternate therapy for women who are unable to take UDCA. This therapy is generally less effective:
  - Hydroxyzine



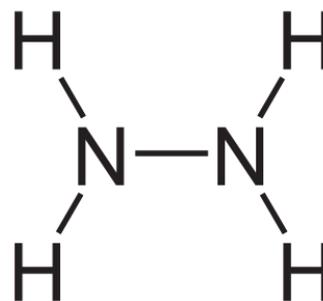
**SAMe**



**Rifampin**



**Cholestyramine**



**Hydrazine**

National Center for Biotechnology Information. PubChem Database. Cholestyramine, CID=70695641, <https://pubchem.ncbi.nlm.nih.gov/compound/Cholestyramine> (accessed on Dec. 8, 2019)

# ICP Maternal Treatment if UDCA Alone is Ineffective



Here are more details on SAmE:



## 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 [76].
- 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 [77].
- 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 [78].

# ICP Maternal 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 [79].

## ICP Maternal Treatment if UDCA Alone is Ineffective



Here are some details on Rifampin. Click through the 3 screens to learn more.

### Rifampin (also know as rifampicin)

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

1 of 3 >



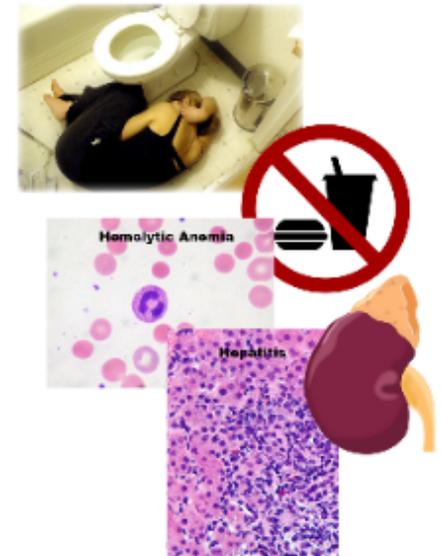
# ICP Maternal Treatment if UDCA Alone is Ineffective



Here are some details on Rifampin. Click through the 3 screens to learn more.

Medication side effects include:

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



2 of 3 >



## ICP Maternal Treatment if UDCA Alone is Ineffective



Here are some details on Rifampin. Click through the 3 screens to learn more.

In the previously mentioned study of fewer than 30 patients, a total daily dose range from 300 to 1200mg orally administered in divided doses were identified as having improvement in pruritus. Infants of these patients were delivered between about 32 and 37 weeks gestation with good perinatal outcomes.

**3 of 3**



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



# ICP Maternal Treatment if UDCA Alone is Ineffective

There are not trials on women with ICP who use these medications. These treatment options did not improve laboratory abnormalities.



**Hydroxyzine**  
The dose is 25mg orally every 6 to 8 hours to treat pruritus with minimal efficacy, but causes sedation for sleep.



# ICP Maternal Treatment if UDCA Alone is Ineffective

There are not trials on women with ICP who use these medications. These treatment options did not improve laboratory abnormalities.



## Chlorpheniramine

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

2 of 4



## ICP Maternal Treatment if UDCA Alone is Ineffective

There are not trials on women with ICP who use these medications. These treatment options did not improve laboratory abnormalities.



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

3 of 4



## ICP Maternal Treatment if UDCA Alone is Ineffective

There are not trials on women with ICP who use these medications. These treatment options did not improve laboratory abnormalities.



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 [82].

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

4 of 4



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



## ICP Pregnancy Management - Antepartum



**Here are some ways to manage ICP during the antepartum period:**

Fetal testing to identify fetus at risk for demise when ICP is diagnosed is unproven. Fetal demise in women with ICP is thought to be a sudden event rather than a chronic placental vascular process so fetal nonstress tests (NST), biophysical profile score (BPP), and daily fetal kick counts may not identify those fetus's at risk for demise [1, 87, 89]. However, because of lack of evidence the value of fetal testing, or mechanism of fetal demise, antepartum is performed.

1 of 2



# ICP Pregnancy Management - Antepartum



**Here are some ways to manage ICP during the antepartum period:**

Twice weekly modified BPP is standard of care in all pregnancies with ICP.

Fetal NSTs in patients with ICP did not identify an increase in abnormal findings in those who went on to have a fetal demise in one study [83].

Other studies reported intrauterine fetal demise occurred within a few days of a reactive NST [84-90].

2 of 2

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



# ICP Pregnancy Management - Time of Delivery

A retrospective cohort study determined the risk of perinatal mortality, stillbirth and infant death, with delivery versus expectant management by gestation age week 34 and 40 weeks of gestation [91].

Gestation Period	Delivery	Expectant Management
37 Weeks	12.3 ████████████████████	21.7 ████████████████████ ████████
38 Weeks	13.7 ████████████████████	23.1 ████████████████████ ██████████████
39 Weeks	18.3 ████████████████████ ████	33.6 ████████████████████ ████████████████ ████

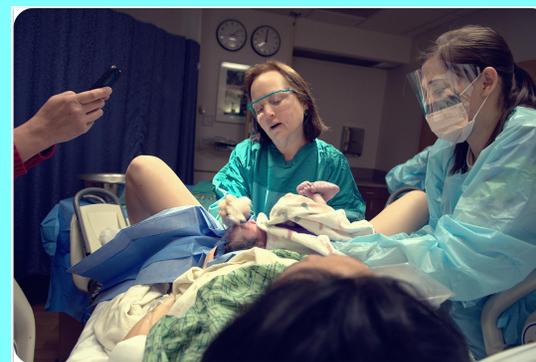
A California study between 2005 and 2008 were analyzed in women with ICP. Fetal, neonatal, and infant mortality was lowest when delivered at 36 weeks gestation and lower than mortality with expectant management at 36 weeks. This observation of lower mortality with delivery versus expectant management occurred when at 37 weeks of gestation (12.3 versus 21.7 per 10,000 fetuses at risk, 38 weeks gestation (13.7 versus 23.1 per 10,000 fetuses at risk, 39 weeks 18.3 versus 33.6 per 10,000 fetuses at risk. This study had limitations; no information on maternal bile acid or transaminase levels, gestation age at the onset of the disease, treatment, and the number of deaths.

# ICP Pregnancy Management



**Here are some  
delivery  
considerations:**

Most women with ICP are delivered at 36+0 to 36+6 weeks gestation or upon diagnoses with ICP if greater than 37+0 weeks of gestation. The decision to deliver is to reduce the risk of fetal demise and so disease resolution can begin for the woman.



## ICP Pregnancy Management



Here are some  
delivery  
considerations:

Delivery should be considered prior to 36 weeks gestation in women with ICP and:

- Jaundice
- Total serum bile acid concentration  $\geq 100\mu\text{mole/L}$  [60, 92, 93].

The bile acid concentration can take several days for results even in major laboratories, which makes it a impractical tool to identify immediate risk [94].



2 of 2



Use the arrows below to move forward with the lesson.



## ICP Pregnancy Management



### Counseling prior to an early 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.
- All women are educated on the limits of fetal lung maturity testing to predict neonatal status.
- If the woman consents to an early delivery after receiving this counseling, a course of antenatal corticosteroids are given prior to delivery.

## ICP Guidelines from Professional Organizations

### **The American College of Obstetricians and Gynecologists**

Recommends delivery at 36+0 to 37+0 weeks of gestation or at diagnosis if diagnosed at term [100].

### **The Royal College of Obstetricians and Gynecologists**

Justifies offering women induction of labor after 37+0 week of gestation, especially those with severe laboratory abnormalities [95].

1 of 2 >>



## ICP Guidelines from Professional Organizations

### The Society for Maternal-Fetal Medicine

States that evidence based recommendation is not available for the timing of delivery when ICP is present. Most management strategies advocate for delivery between 37 and 38 weeks gestation and sooner with documented pulmonary maturity and prior obstetrical history, antenatal testing, and gestational age are to be considered [96]. This opinion is based on three studies comparing pregnancy with and those not complicated by ICP [57,97,98]. The Society for Maternal-Fetal Medicine did not consider bile acid level to guide their recommendation but cited a study supporting expectant management of mild ICP with a bile acid  $<40\mu\text{mol/L}$ .

2 of 2 ➡➡

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

# ICP Delivery Recommendations



Here are some delivery recommendations for pregnant women with ICP:

- 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 [99, 101].
- Vitamin K is not routinely evaluated prior to delivery; however the prothrombin time (PT) can be checked and vitamin K administered if prolonged [102, 103].
- Increased cesarean delivery rates are not noted with induction of labor compared with expectant management.
- A meta-analysis including non-randomized studies found no difference in cesarean section rates associated with use of UDCA [110].

# ICP Postpartum Maternal Management



Here are some management considerations for ICP in the postpartum period:

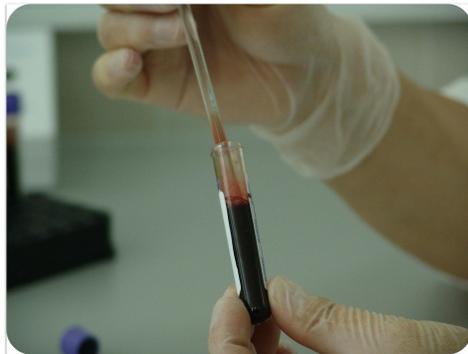


- Pruritus generally resolves in a few days following delivery.
- Serum bile acid concentrations and liver function tests are normalized in the first few days following delivery.
- Women with ICP can breastfeed without complications. UDCA is noted in low levels in breast milk; therefore, small amounts will be ingested by the infant but not expected to cause adverse effects in the infant [104].

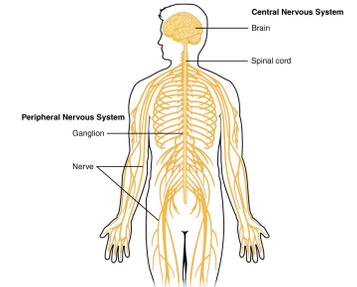
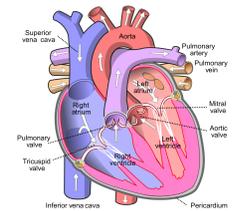
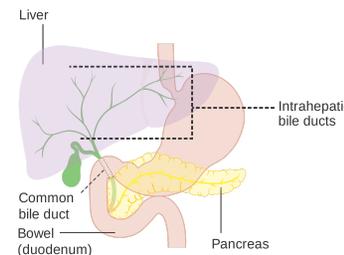
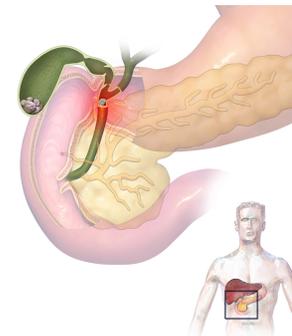
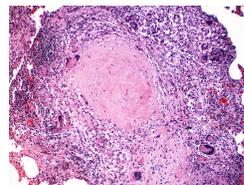
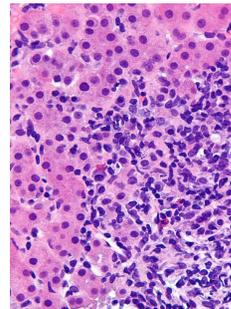
# ICP Postpartum Monitoring

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.



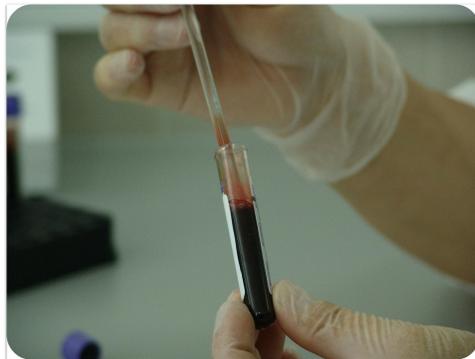
Studies suggest ICP may be associated with [\[34\]](#), [\[35\]](#), [\[105\]](#), [\[106\]](#):  
**Click the pictures for the associations.**



# ICP Postpartum Monitoring

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

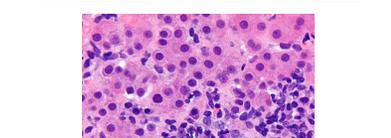
If either blood test does not return to normal, referral to a hepatologist is recommended to evaluate for hepatobiliary diseases.



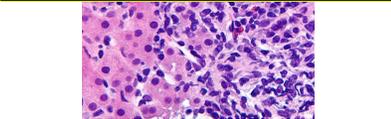
Studies suggest ICP may be associated with [34, 35, 105, 106]:  
 Click the pictures for the associations.



**Gallstone Disease**



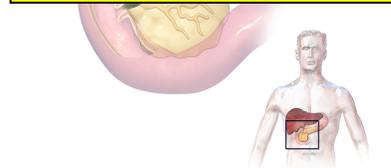
**Hepatitis C**



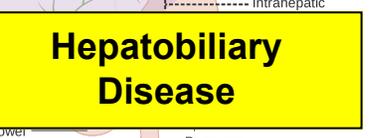
**Fibrosis**



**Cholangitis**



**Hepatobiliary Disease**



**Cardiovascular Disease**



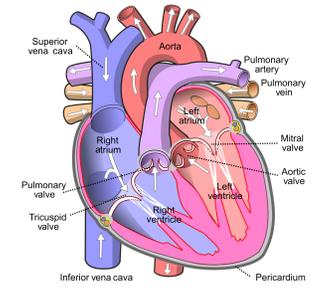
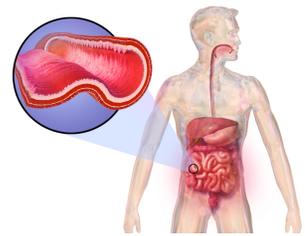
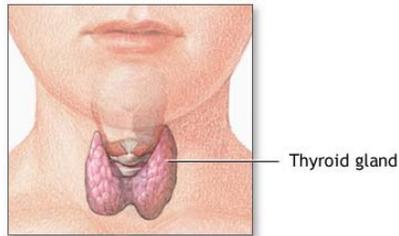
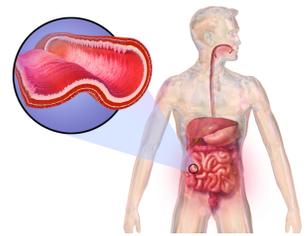
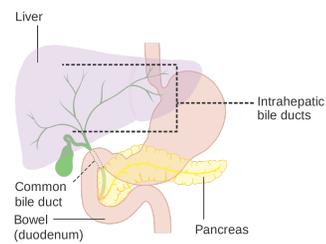
**Immune-Mediated Disease**

# ICP Postpartum Monitoring



**A Swedish registry-based study of 11,000 postpartum women who developed ICP in her pregnancy with over 113,000 women who delivered without ICP, ICP was associated with [106]:**

**Click the pictures for the associations**

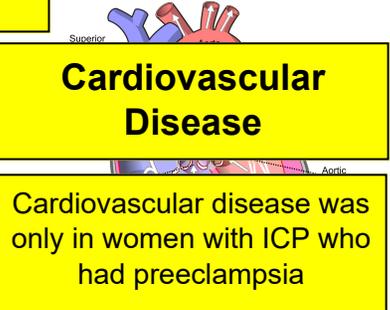
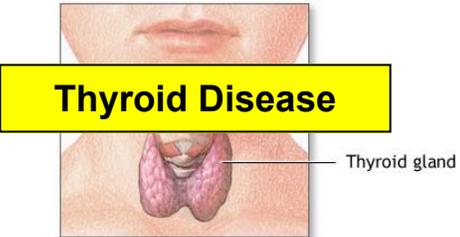
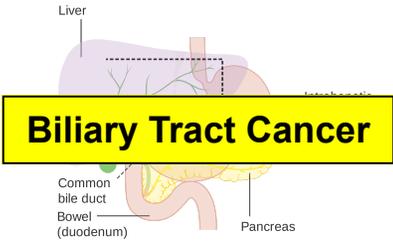


# ICP Postpartum Monitoring



**A Swedish registry-based study of 11,000 postpartum women who developed ICP in her pregnancy with over 113,000 women who delivered without ICP, ICP was associated with [106]:**

**Click the pictures for the associations**



## 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 for her.
- 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 [107].
- 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 Postpartum Contraception



- Progestin-only contraception is an acceptable choice for women with history of ICP or cholestasis related to estrogen-progestin contraception per CDC [107].
- Progestin-only contraception is not associated with recurrent 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, elevated aminotransferases, both, and the absence of diseases that cause similar symptoms and laboratory abnormalities.
  - 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.
- If UDCA is started, elevated bile acid and transaminase level may not be noted.

## ICP Summary and Recommendations

- The differential diagnosis of symptoms must be considered.
  - Elevated transaminase levels are noted in HELLP syndrome, preeclampsia with severe features, and acute fatty liver of pregnancy.
  - 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 respiratory distress syndrome (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 checked at least weekly 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 she delivers.
- Delivery if pregnancy  $\geq$ 37 weeks gestation.

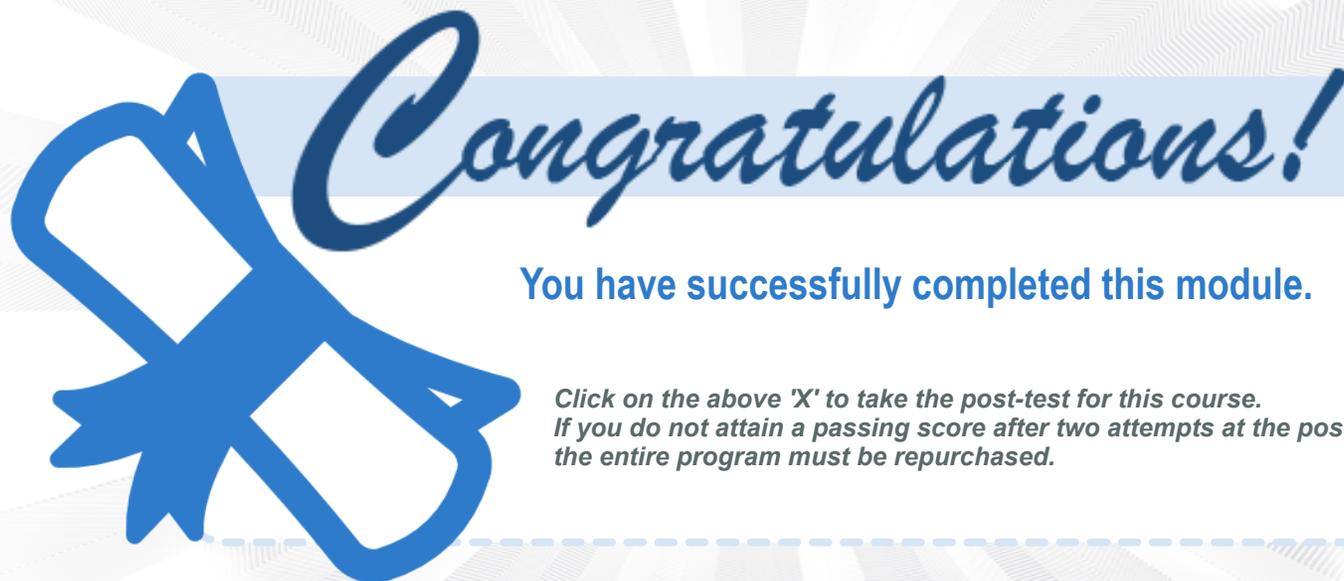
## ICP Summary and Recommendations

- The goal is to deliver women with ICP at 36 weeks gestation; unless diagnosed after 36 weeks gestation then deliver immediately. Delivery may occur earlier than 36 weeks gestation in complicated cases.
- Serum bile acids and liver function levels are checked 6 to 8 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>



You have successfully completed this module.

*Click on the above 'X' to take the post-test for this course.  
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. Abedin P, Weaver JB, Egginton E. [Intrahepatic cholestasis of pregnancy: prevalence and ethnic distribution](#). *Ethn Health* 1999; 4:35.
9. Gonzalez MC, Reyes H, Arrese M, et al. [Intrahepatic cholestasis of pregnancy in twin pregnancies](#). *J Hepatol* 1989; 9:84.
10. Savander M, Ropponen A, Avela K, et al. [Genetic evidence of heterogeneity in intrahepatic cholestasis of pregnancy](#). *Gut* 2003; 52:1025.
11. Floreani A, Gervasi MT. [New Insights on Intrahepatic Cholestasis of Pregnancy](#). *Clin Liver Dis* 2016; 20:177.
12. Pataia V, Dixon PH, Williamson C. [Pregnancy and bile acid disorders](#). *Am J Physiol Gastrointest Liver Physiol* 2017; 313:G1.
13. 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.
14. 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.
15. 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.
16. 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.

17. 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.
18. 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.
19. 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.
20. Floreani A, Carderi I, Paternoster D, et al. Intrahepatic cholestasis of pregnancy: three novel MDR3 gene mutations. Aliment Pharmacol Ther 2006; 23:1649.
21. Wasmuth HE, Glantz A, Keppeler H, et al. Intrahepatic cholestasis of pregnancy: the severe form is associated with common variants of the hepatobiliary phospholipid transporter ABCB4 gene. Gut 2007; 56:265.
22. 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.
23. Dixon PH, Williamson C. The pathophysiology of intrahepatic cholestasis of pregnancy. Clin Res Hepatol Gastroenterol 2016; 40:141.
24. Keitel V, Vogt C, Häussinger D, Kubitz R. Combined mutations of canalicular transporter proteins cause severe intrahepatic cholestasis of pregnancy. Gastroenterology 2006; 131:624.
25. Van Mil SW, Milona A, Dixon PH, et al. Functional variants of the central bile acid sensor FXR identified in intrahepatic cholestasis of pregnancy. Gastroenterology 2007; 133:507.
26. Sookoian S, Castaño G, Burgueño A, et al. Association of the multidrug-resistance-associated protein gene (ABCC2) variants with intrahepatic cholestasis of pregnancy. J Hepatol 2008; 48:125.
27. Wånggren K, Sparre LS, Wrambsy H. Severe jaundice in early IVF pregnancy. Eur J Obstet Gynecol Reprod Biol 2004; 112:228.
28. 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.
29. 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.
30. 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.

31. Davies MH, Ngong JM, Yucesoy M, et al. The adverse influence of pregnancy upon sulphation: a clue to the pathogenesis of intrahepatic cholestasis of pregnancy? J Hepatol 1994; 21:1127.
32. Bacq Y, Sapey T, Bréchet MC, et al. Intrahepatic cholestasis of pregnancy: a French prospective study. Hepatology 1997; 26:358.
33. 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.
34. 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.
35. 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.
36. Leevy CB, Koneru B, Klein KM. Recurrent familial prolonged intrahepatic cholestasis of pregnancy associated with chronic liver disease. Gastroenterology 1997; 113:966.
37. Turunen K, Mölsä A, Helander K, et al. Health history after intrahepatic cholestasis of pregnancy. Acta Obstet Gynecol Scand 2012; 91:679.
38. 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.
39. Kondrackiene J, Kupcinskas L. Intrahepatic cholestasis of pregnancy-current achievements and unsolved problems. World J Gastroenterol 2008; 14:5781.
40. 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.
41. 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.
42. Kenyon AP, Piercy CN, Girling J, et al. Obstetric cholestasis, outcome with active management: a series of 70 cases. BJOG 2002; 109:282.
43. Furrer R, Winter K, Schäffer L, et al. Postpartum Blood Loss in Women Treated for Intrahepatic Cholestasis of Pregnancy. Obstet Gynecol 2016; 128:1048.
44. 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.

45. Diken Z, Usta IM, Nassar AH. A clinical approach to intrahepatic cholestasis of pregnancy. Am J Perinatol 2014; 31:1.
46. Huang WM, Gowda M, Donnelly JG. Bile acid ratio in diagnosis of intrahepatic cholestasis of pregnancy. Am J Perinatol 2009; 26:291.
47. Rolfes DB, Ishak KG. Liver disease in pregnancy. Histopathology 1986; 10:555.
48. 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.
49. 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. Cochrane Database Syst Rev 2019; 7:CD012546.
50. 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.
51. 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.
52. 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.
53. Atabey S, Duvan CI, Eren U, Turhan NO. Intrahepatic cholestasis and eclampsia: a case report. Hypertens Pregnancy 2007; 26:363.
54. Raz Y, Lavie A, Vered Y, et al. Severe intrahepatic cholestasis of pregnancy is a risk factor for preeclampsia in singleton and twin pregnancies. Am J Obstet Gynecol 2015; 213:395.e1.
55. Marathe JA, Lim WH, Metz MP, et al. A retrospective cohort review of intrahepatic cholestasis of pregnancy in a South Australian population. Eur J Obstet Gynecol Reprod Biol 2017; 218:33.
56. 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.
57. 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.
58. Geenes V, Lövgren-Sandblom A, Benthin L, et al. The reversed fetomaternal bile acid gradient in intrahepatic cholestasis of pregnancy is corrected by ursodeoxycholic acid. PLoS One 2014; 9:e83828.

59. 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.
60. 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.
61. 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.
62. 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.
63. 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.
64. 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.
65. 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.
66. 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.
67. Kremer AE, Oude Elferink RP, Beuers U. Pathophysiology and current management of pruritus in liver disease. *Clin Res Hepatol Gastroenterol* 2011; 35:89.
68. Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. *Obstet Gynecol* 2014; 124:120.
69. Pusi T, Beuers U. Intrahepatic cholestasis of pregnancy. *Orphanet J Rare Dis* 2007; 2:26.
70. 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.
71. 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.
72. Bacq Y, Sentilhes L, Reyes HB, et al. Efficacy of ursodeoxycholic acid in treating intrahepatic cholestasis of pregnancy: a meta-analysis. *Gastroenterology* 2012; 143:1492.

73. Gurung V, Middleton P, Milan SJ, et al. [Interventions for treating cholestasis in pregnancy](#). *Cochrane Database Syst Rev* 2013; CD000493.
74. Kong X, Kong Y, Zhang F, et al. [Evaluating the effectiveness and safety of ursodeoxycholic acid in treatment of intrahepatic cholestasis of pregnancy: A meta-analysis \(a prisma-compliant study\)](#). *Medicine (Baltimore)* 2016; 95:e4949.
75. Chappell LC, Bell JL, Smith A, et al. Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): a randomised controlled trial. *Lancet* 2019; 394:849.
76. Ozkan S, Ceylan Y, Ozkan OV, Yildirim S. [Review of a challenging clinical issue: Intrahepatic cholestasis of pregnancy](#). *World J Gastroenterol* 2015; 21:7134.
77. 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.
78. 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.
79. Mela M, Mancuso A, Burroughs AK. [Review article: pruritus in cholestatic and other liver diseases](#). *Aliment Pharmacol Ther* 2003; 17:857.
80. Liu J, Murray AM, Mankus EB, et al. [Adjuvant Use of Rifampin for Refractory Intrahepatic Cholestasis of Pregnancy](#). *Obstet Gynecol* 2018; 132:678.
81. 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.
82. 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.
83. Fisk NM, Storey GN. [Fetal outcome in obstetric cholestasis](#). *Br J Obstet Gynaecol* 1988; 95:1137.
84. 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.
85. Laatikainen T, Tulenheimo A. [Maternal serum bile acid levels and fetal distress in cholestasis of pregnancy](#). *Int J Gynaecol Obstet* 1984; 22:91.
86. Sentilhes L, Verspyck E, Pia P, Marpeau L. [Fetal death in a patient with intrahepatic cholestasis of pregnancy](#). *Obstet Gynecol* 2006; 107:458.
87. Lee RH, Incerpi MH, Miller DA, et al. [Sudden fetal death in intrahepatic cholestasis of pregnancy](#). *Obstet Gynecol* 2009; 113:528.

88. 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.
89. Saleh MM, Abdo KR. Consensus on the management of obstetric cholestasis: National UK survey. BJOG 2007; 114:99.
90. 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.
91. Puljic A, Kim E, Page J, et al. The risk of infant and fetal death by each additional week of expectant management in intrahepatic cholestasis of pregnancy by gestational age. Am J Obstet Gynecol 2015; 212:667.e1.
92. 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.
93. 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.
94. Egerman RS, Riely CA. Predicting fetal outcome in intrahepatic cholestasis of pregnancy: is the bile acid level sufficient? Hepatology 2004; 40:287.
95. Obstetric Cholestasis (Green-top Guideline No. 43)  
<https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg43/>.
96. <https://www.smfm.org/publications/96-understanding-intrahepatic-cholestasis-of-pregnancy> (Accessed on October 19, 2017).
97. Roncaglia N, Arreghini A, Locatelli A, et al. Obstetric cholestasis: outcome with active management. Eur J Obstet Gynecol Reprod Biol 2002; 100:167.
98. Fisk NM, Bye WB, Storey GN. Maternal features of obstetric cholestasis: 20 years experience at King George V Hospital. Aust N Z J Obstet Gynaecol 1988; 28:172.
99. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. Hepatology 2004; 40:467.
100. American College of Obstetricians and Gynecologists. ACOG committee opinion no. 764: Medically indicated Late-Preterm and Early-Term Deliveries. Obstet Gynecol 2019.
101. Oztekin D, Aydal I, Oztekin O, et al. Predicting fetal asphyxia in intrahepatic cholestasis of pregnancy. Arch Gynecol Obstet 2009; 280:975.
102. 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.

103. DeLeon A, De Oliveira GS, Kalayil M, et al. The incidence of coagulopathy in pregnant patients with intrahepatic cholestasis: should we delay or avoid neuraxial analgesia? J Clin Anesth 2014; 26:623.
104. <https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~oV4054:1> (Accessed on August 16, 2017).
105. Hirvioja ML, Kivinen S. Inheritance of intrahepatic cholestasis of pregnancy in one kindred. Clin Genet 1993; 43:315.
106. 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.
107. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. MMWR Recomm Rep 2016; 65:1.
108. 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
109. 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
110. 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.