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INTRAHEPATIC CHOLESTASIS OF PREGNANCY
MANAGEMENT GUIDELINES
Alaska Native Medical Center

Background

Intrahepatic cholestasis of pregnancy (ICP) is a common disorder in our obstetric population, with an incidence of 4.9% on a recent chart survey. Symptoms usually develop in the third trimester, characterized by severe pruritus without a rash.

'Severe' pruritus is characterized by pruritus, which may be intolerable. It is often generalized but predominates on the palms and the soles of the feet and is worse at night. At minimum there should be a history of insomnia due to the constant scratching, including the soles and palms, observed scratching during clinical encounters, and excoriations found on exam.

The pathophysiology involves abnormal bile acid metabolism, with deposition of bile acids in the maternal tissues and the placenta. It is commonly (approximately 70% of cases) accompanied by elevated maternal serum total bile acids (over 10 umol/L) with a predominance of the unconjugated, or cholic acid, fraction (Cholic acid $\geq$ 3 umol/L). Abnormal liver function tests (transaminase levels in the 60-200 range U/L, and alkaline phosphatase 200-400 U/L range) are typically present, although hyperbilirubinemia with clinical jaundice is uncommon.

Apart from the severe maternal symptomatology, the chief perinatal risk is intrauterine fetal demise (incidence 1-9%), which is typically very poorly predicted by antenatal fetal surveillance. Late preterm birth (34-36 weeks), fetal intolerance of labor, and meconium-stained fluid are also more common in these pregnancies. Maternal symptoms resolve promptly after delivery, but there is a 40-70% recurrence rate in subsequent pregnancies. In a review of over 1 million women, it was found that intervention at a TBA of > 40 show benefit outweighing the risks. (Geenes 2014)

Many pregnant women will have itching without abnormal laboratory results. In our own data set this characterized 23% of women. In ICP, severe pruritus will often antedate elevation of serum bile acids by 2-4 weeks. Women with mild pruritus but normal bile acids x 2 should be classified as "pruritus gravidarum". These women will usually not be scratching during their clinical encounters, not be found to be excoriated, will not give a history of insomnia due to the constant itching, and have not required medical treatment.

In contrast, 'Severe Pruritus of Pregnancy' includes those patients with severe pruritus with TBA < 10.
There are three subcategories:
-Severe Pruritus of Pregnancy: on Ursodiol
-Severe Pruritus of Pregnancy: not on Ursodiol
-Severe Pruritus of Pregnancy: other lab criteria (see non-bile acid metrics below)

The Severe Pruritus of Pregnancy category includes those patients with severe pruritus who have normal bile acids and liver functions but have been started on ursodiol empirically by another provider. These women no longer have severe symptoms and have TBA < 10. Generally, one should wait to have the diagnosis confirmed before starting ursodiol. (Ursodiol will lower serum bile acids and then make it impossible to establish the diagnosis.) In this case the final diagnosis will need to be a clinical decision of the individual provider dependent on assessment of severity of the symptoms.

Lastly, it is not entirely clear from the literature which total bile acid level to plan the patient's delivery on, e. g., the maximum TBA or the most recent TBA just before delivery (a.k.a. 'proximate' TBA). After reviewing dozens of articles, most of the papers do not explicitly state which level they use (Maximum TBA vs proximate TBA).

Of the papers which do mention which TBA they use - the maximum level is the most frequently mentioned. (12, 16, 24, 25, 26) Ironically when some the papers that use the maximum level as a cut-off do mention their patient's proximate TBA, the proximate level was almost identical to the maximum level. This suggests their patients did not actually take their ursodiol, which should have significantly decreased the TBA.

In any case, once a patient has started ursodiol her TBAs will decrease, so that factor alone would underscore the need to use the maximum TBA and would be a better marker than the current medicated TBA.

Considering the sparse data at this time, as a department we have decided to use the MAXIMIMUM total bile acid level to determine management, until a better marker is developed in the literature.

Management

a. Diagnosis

1. Patients in our population should be asked about severe itching in previous pregnancies and their records reviewed to see if the diagnosis of ICP was suspected.
2. Patients who present with symptoms of severe pruritus, but without an obvious rash, may or may not have ICP, and require a workup.
3. An attempt should be made to confirm the diagnosis by obtaining a random total bile acids level and liver function tests.
4. There is only a need for fractioned bile acids if the patient had been started on ursodiol due to severe symptoms prior to lab results returned.
5. Patients in our population with a history of a prior stillbirth should also be considered for screening for ICP in the early third trimester.

b. Diagnostic Categories (See also Table 1)

Severe ICP-A TBA > 100

Severe ICP-B	TBA $\geq$ 40 < 100	
Mild ICP	TBA $\geq$ 10 < 40	
Severe Pruritus -on Ursodiol	TBA < 10	
Severe Pruritus - other lab criteria	TBA < 10	(See non-bile acid metrics)
Severe Pruritus - not on Ursodiol	TBA < 10	
Pruritus Gravidarum*	TBA < 10	

Other considerations

-If two sets of bile acids and liver functions are normal, the patient's symptoms are severe, and they are not taking ursodiol - then they are diagnosed with 'Severe Pruritus of Pregnancy - not on Ursodiol'. (Table 1, Figure 1)

-*If two sets of bile acids and liver functions are normal and the patient's symptoms are not severe, they are diagnosed with 'Pruritus Gravidarum'. (Table 1, Figure 1)

-If the patient $\leq$ 32 wks with prior severe pruritus has already been started on ursodiol for 'Severe Pruritus of Pregnancy', but has normal labs q wk x2, then discontinue the ursodiol and continue weekly labs.

-If the pruritus remains severe and the TBA < 10, then follow this patient as 'Severe Pruritus of Pregnancy – not on Ursodiol'. (Table 1, Figure 1)

-If the pruritus becomes non-severe and the TBA < 10, then follow this patient as 'Pruritus Gravidarum'. (Table 1, Figure 1)

-If liver functions are elevated, but TBA < 10, then serologic studies for hepatitis should be obtained. (Women with hepatitis A are usually symptomatic with nausea, malaise, jaundice, etc.... but do not usually have pruritus.)

-Cholelithiasis is also more common in women with ICP, but the symptoms are usually quite different (abdominal and shoulder pain, vomiting, etc, but usually not pruritus).

b. Therapy

1. The current mainstay of symptomatic therapy is ursodiol, but it is unclear if it improves maternal symptoms or perinatal outcomes. Less than 10% of ursodiol is absorbed, its site of action being in the enterohepatic circulation, where it enhances bile acid excretion. It is an FDA pregnancy class B drug. The starting dose is 15 mg/kg/day, usually divided into 3 doses. If the patient has not experienced relief within a week, the dose may be increased to 25 mg/kg/day. Ursodiol is manufactured as 300 mg capsules and the dose may be rounded off as convenient.
2. Women who have severe symptoms and have normal bile acids, should wait to have the diagnosis confirmed before starting ursodiol. (Ursodiol will lower serum bile acids and then make it impossible to establish the diagnosis.) The final diagnosis will need to be a clinical decision of the individual provider dependent on assessment of severity of the symptoms.
3. Other agents to consider are rifampin or cholestyramine.
   -The total daily dose of rifampin ranges from 300 to 1200 mg, administered in divided doses. Pruritus improved in most patients and many had a reduction in bile acid and/or transaminase levels.
   -Cholestyramine is given orally in divided doses starting at 2 to 4 g per day and gradually increased to a maximum dose of 16 g per day, if needed for symptom control. However,

its effect on pruritus in ICP is limited and cholestyramine may cause constipation, abdominal discomfort, and malabsorption of fat including fat-soluble vitamins (eg, vitamin K), especially at high doses (eg, >4 grams per day).

4. Antihistamine therapy with diphenhydramine or hydroxyzine is typically *not* effective for symptom relief. However, administration of these drugs at bedtime, when symptoms are usually worse, may help the mother to sleep, as they usually produce drowsiness.

c. Laboratory monitoring

1. If a patient is taking ursodiol (ursodeoxycholic acid) and your lab reports ursodeoxycholic acid in the fractionated results, then please subtract the synthetic ursodeoxycholic acid to produce an amended TBA which does not reflect the medication the patient is taking.
2. In known ICP with TBAs < 100: total bile acids and LFTs should be monitored on a weekly basis after 36 wks.
3. In Severe pruritus of pregnancy: total bile acids and LFTs should be monitored on a weekly basis.
4. In Pruritus Gravidarum: total bile acids and LFTs should be monitored on a q 2 week basis until negative x2.

d. Non-total bile acid metrics

From 2003-2013 the ANMC MFM and OB/GYN departments performed an extensive Quality Improvement evaluation as we learned about the high prevalence of ICP in our population. Among other things we learned that the total bile acid level often lagged behind the symptoms of severe pruritus by 2 to several weeks. The delay in the bile acid tests themselves is compounded by the time lag for obtaining the results.

We also learned that the following indicators became positive in association with severe symptoms before the total bile acids were elevated. As such, we use the following non-total bile acid metrics as an indication for delivery at 39 weeks and weekly NSTs- if the patient did not have hepatitis, steatosis, or cholelithiasis.

Cholic acid $\geq$ 3 umol/L (If fractionated bile acids had been obtained)

Total Bilirubin
$\geq$ 1.0 mg/dL

AST 2x normal lab limits

ALT 2x normal lab limits

Alk. phosphatase
$\geq$ 300 U/L

e. Fetal Surveillance

1. Women with a diagnosis of ICP should undergo fetal surveillance beginning at 32 weeks. The patient should also be instructed in recording daily fetal kick counts. (Table 1)
2. Patients who present with uncertain dates should have an initial dating ultrasound, followed by a repeat ultrasound in 3 weeks to confirm the due date (if feasible within the time frame of the pregnancy), and help establish the time for induction. If doubt still exists as to the actual EDD, amniocentesis for fetal lung maturity may be offered at the discretion of the provider, or after consultation with MFM as indicated.
3. Patients with pruritus gravidarum should receive bile acid and LFT testing q 2 wks until negative x2, but no antenatal testing nor early delivery for this indication alone.

Severe ICP-A	TBA > 100	BPP/wk and NST 2x /wk
Severe ICP-B	TBA ≥ 40 < 100	BPP/wk and NST /wk
Mild ICP	TBA ≥ 10 < 40	BPP/wk and NST /wk
Severe Pruritus -on Ursodiol	TBA < 10	NST /wk
Severe Pruritus - other lab criteria	TBA < 10	NST /wk
Severe Pruritus - not on Ursodiol	TBA < 10	No testing
Pruritus Gravidarum*	TBA < 10	No testing

f. Delivery

Due to the risk of intrauterine demise, it is recommended that women with the criteria below receive early delivery based on these management plans.

		Ripen / Delivery Range
Severe ICP-A	TBA ≥ 100	36 - 36 6/7
Severe ICP-B	TBA ≥ 40 < 100	37 - 37 6/7
Mild ICP	TBA ≥ 10 < 40	38 - 38 6/7
Severe Pruritus -on Ursodiol	TBA < 10	39 - 39 6/7
Severe Pruritus - other lab criteria	TBA < 10	39 - 39 6/7
Severe Pruritus - not on Ursodiol	TBA < 10	39 - 39 6/7
Pruritus Gravidarum	TBA < 10	Other obstetric indications

Other

-Those ICP patients delivering at field facilities, if the maximum TBA ≥ 10 < 40, then cervical ripening or delivery can begin at 39 0/7.

-If the maximum TBA is ≥ 40 then the field patient should be referred to ANMC at 37 0/7

-Women with an unfavorable cervix are candidates for out-patient pre-induction cervical ripening with misoprostol if fetal surveillance is reassuring.

-Draw bile acids and LFTs on all categories of patients upon admission to L/D, except Pruritus Gravidarum

-Post-partum:

-Patients with TBA ≥ 10 during pregnancy should get repeat TBAs at 6 wk PP. If the postpartum TBA ≥ 10, then refer to Hepatology

-Hormonal contraception may be offered, as very few women will have recurrence of symptoms on such therapy.

-Patients in our population with a history of a prior stillbirth should be considered for screening for ICP in the early third trimester.

Table 1			
History, symptoms, signs	Lab abnormalities*	Prior Treatment	Current Treatment
Severe ICP-A			
(Any one of these) History Generalized 'severe' pruritus -intolerable -predominates on the palms and the soles of the feet -worse at night -history of insomnia due to the constant scratching Exam -observed scratching during clinical encounters -excoriations found on exam	Maximum TBA ≥ 100		Ursodiol starting at 15 mg/kg divided BID BPP q wk NST 2x/wk Cervical ripening or cesarean delivery at 36 0/7 -36 6/7 wks
Severe ICP-B			
History and exam as above	Maximum TBA ≥ 40 <100		Ursodiol starting at 15 mg/kg divided BID TBA and LFTs q wk p 36 wk BPP q wk NST q wk Cervical ripening or

			cesarean delivery at 37 0/7 -37 6/7 wks
Mild ICP			
History and exam as above	TBA ≥ 10 < 40		Ursodiol starting at 15 mg/kg divided BID TBA and LFTs q wk p 36 wk BPP q wk NST q wk Cervical ripening or cesarean delivery at 38 0/7 – 38 6/7 wks
Severe Pruritus of Pregnancy – on ursodiol			
History and exam as above	TBA < 10	If ≤ 32 wks with prior severe pruritus on ursodiol, but has normal labs q wk x2, then discontinue ursodiol and continue weekly labs. -if TBAs become abnormal, then deliver per TBA level -if sx become non-severe off ursodiol and repeat BA are normal, then treat as pruritus gravidarum	TBA and LFTs q wk NST q wk -perform cervical ripening or cesarean delivery at 39 0/7 - 39 6/7 weeks
Severe Pruritus of Pregnancy – not on ursodiol			
History and exam as above	TBA < 10	Off ursodiol	TBA and LFTs q wk

		-if TBAs become abnormal, then deliver per TBA level -if sx become non-severe off ursodiol and repeat BA are normal, then treat as pruritus gravidarum	No antenatal testing -perform cervical ripening or cesarean delivery at 39 0/7 - 39 6/7 weeks
Severe Pruritus of Pregnancy – other lab criteria			
History and exam as above	TBA < 10 Any one of these: Cholic acid $\geq$ 3 umol/L Total Bilirubin $\geq$ 1.0 mg/dL AST 2x normal lab limits ALT 2x normal lab limits Alk. phosphatase $\geq$ 300 U/L -no evidence of steatosis, hepatitis, or cholelithiasis		Ursodiol starting at 15 mg/kg divided BID TBA and LFTs q wk NST q wk -perform cervical ripening or cesarean delivery at 39 0/7 - 39 6/7 weeks
Pruritus gravidarum			
Pruritus, but non-severe	TBA < 10	Not on ursodiol	TBA and LFTs q 2 wks until negative x2 No antenatal testing Delivery for usual obstetric indications

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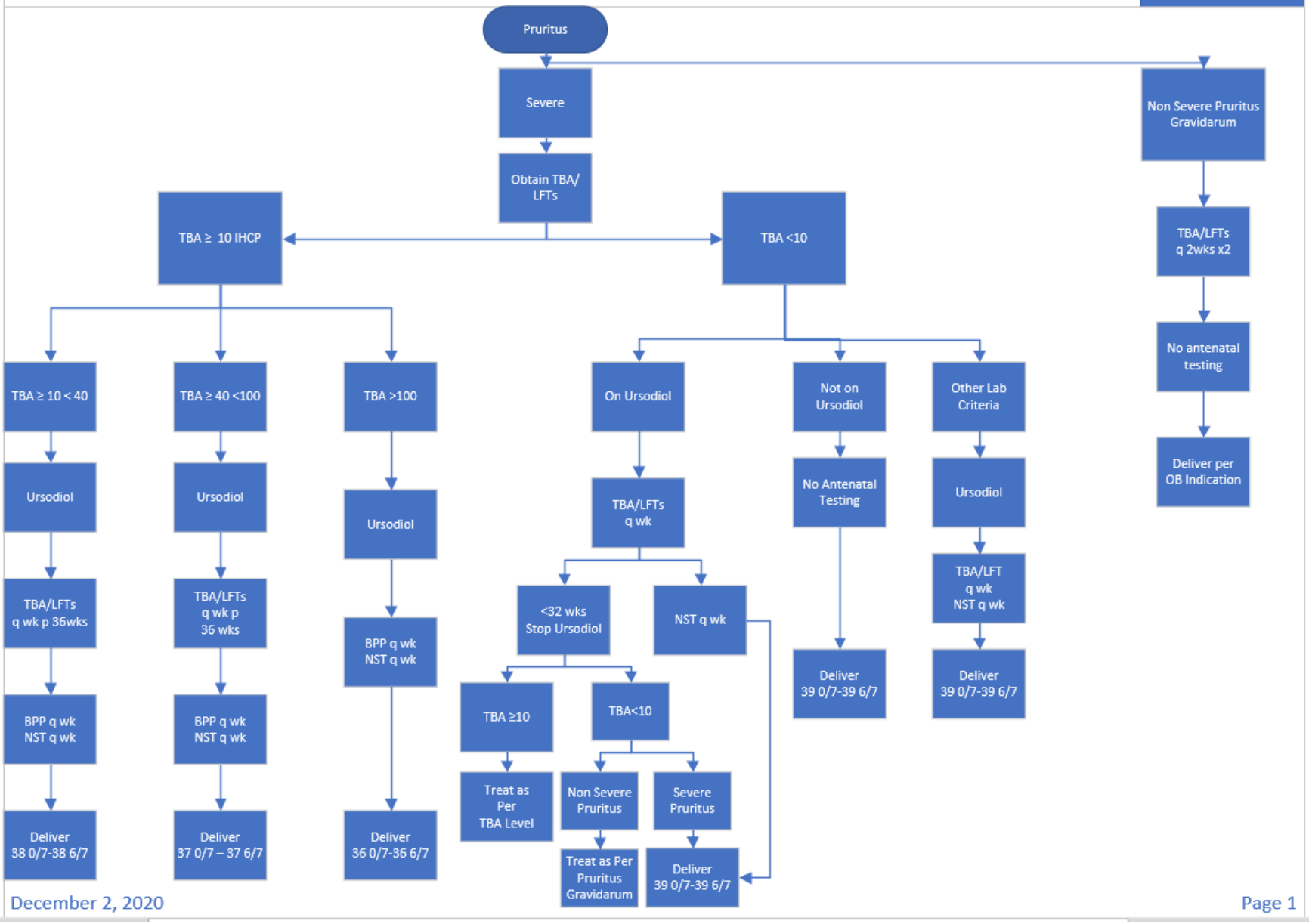
Pruritus


Pruritus
Severe
Obtain TBA/ LFTs
Non Severe Pruritus Gravidarum
TBA/LFTs q 2wks x2
No antenatal testing
Deliver per OB Indication
TBA ≥ 10 IHCP
TBA <10
TBA ≥ 10 < 40
TBA ≥ 40 <100
TBA >100
Ursodiol
TBA/LFTs q wk p 36wks
BPP q wk NST q wk
Deliver 38 0/7-38 6/7
TBA/LFTs q wk p 36 wks
Deliver 37 0/7 – 37 6/7
BPP q wk NST q wk
Deliver 36 0/7-36 6/7
On Ursodiol
TBA/LFTs q wk
<32 wks Stop Ursodiol
NST q wk
TBA ≥10
TBA<10
Treat as Per TBA Level
Non Severe Pruritus
Severe Pruritus
Treat as Per Pruritus Gravidarum
Deliver 39 0/7-39 6/7
Not on Ursodiol
No Antenatal Testing
Deliver 39 0/7-39 6/7
Other Lab Criteria
Ursodiol
TBA/LFT q wk NST q wk
Deliver 39 0/7-39 6/7