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INTRAHEPATIC CHOLESTASIS OF PREGNANCY MANAGEMENT GUIDELINES

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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 $\mu\text{mol/L}$) with a predominance of the unconjugated, or cholic acid, fraction (Cholic acid $> 3 \mu\text{mol/L}$). 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, pruritus will often antedate elevation of serum bile acids by 2-4 weeks. Women with 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.

The last diagnostic category includes those patients with 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 normal bile acids. 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. Discussion with MFM for a “second opinion” is always welcome.

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, the majority 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 light of the sparse data at this time, as a department we have decided to use the MAXIMUM 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 in our population with a history of a prior stillbirth should also be considered for screening for ICP in the early third trimester.
3. Patients who present with symptoms of severe pruritus, but without an obvious rash, may or may not have ICP, and require a workup.
4. An attempt should be made to confirm the diagnosis by obtaining a random total bile acids level and liver function tests.
5. Women with severe pruritus and elevated bile acids and/or liver functions have the disorder and should be managed as below, Table 1, Figure 1 (see Treatment b, c, d).
6. Women with pruritus who have a normal initial bile acids level should have bile acids redrawn in 10-14 days, as the values may increase to diagnostic levels as the pregnancy progresses. The pregnancy should be monitored as presumptively having ICP until the diagnosis is confirmed or disproven. Table 1, Figure 1
7. 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
8. If the patient has already been started on ursodiol by another provider for what was felt to be 'presumptive ICP', but has persistently normal labs, a trial of discontinuing ursodiol may be considered. Repeat the bile acids again after two weeks of being off medication and follow accordingly. Table 1, Figure 1
9. If liver functions are elevated, but bile acids are normal, serologic studies for hepatitis C should be obtained. (Most women already have their hepatitis B serology known, and women with hepatitis A are usually symptomatic with nausea, malaise, jaundice, etc.... but do not usually have pruritus.)
10. 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).

11. A maternal-fetal medicine telephone or formal consult may be considered for women in whom the diagnosis of ICP is entertained. ICP cases should be entered into the existing database for ongoing QI purposes.
12. Severe ICP is defined if the maximum total bile acid is ever ≥ 40 $\mu\text{mol/L}$

b. Therapy

1. The current mainstay of therapy is ursodiol. It is usually quite effective for relief of maternal symptoms, but it is unclear if it improves 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 do not have severe symptoms, and who 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. Discussion with MFM for a “second opinion” is always welcome.
3. 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.
4. Some authorities recommend supplementation with phytonadione (vitamin K) 10 mg orally once a week as prophylaxis for hemorrhagic disease of the newborn, but the evidence is not convincing as to its benefit in this disorder.

c. Bile acid monitoring

1. In ICP total bile acids can be monitored on a weekly basis from 36 wks onward.
2. If the maximum TBA ≥ 40 , then cervical ripening or delivery can be initiated after 37 0/7 wks.
3. If the maximum TBA $\geq 10 < 40$, then cervical ripening or delivery can begin at 39 0/7 at ANMC
4. If the patient is delivering at a field referral facility, then if the TBA $\geq 10 < 20$, then cervical ripening or delivery can begin at 39 0/7. If the maximum TBA is ≥ 20 then the patient should be referred to ANMC at 37 0/7.

d. Fetal Surveillance

1. Women with a diagnosis of ICP should undergo fetal surveillance beginning at 32 weeks because of the risk of intrauterine fetal demise. It is recommended that patients undergo weekly biophysical profiles. The patient should also be instructed in recording daily fetal kick counts.
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 weekly BPP monitoring, but induction of labor need not be scheduled.

e. Delivery

1. Because of the risk of intrauterine demise, it is recommended that women with an established diagnosis of severe ICP (Maximum TBA ≥ 40) can undergo cervical ripening at 37 weeks of gestation (EDD established by early ultrasound, or by establishing dates and/or fetal lung maturity as above).
2. If the maximum TBA $\geq 10 < 40$, then cervical ripening or delivery can begin at 39 0/7 at ANMC
3. If the ICP patient is delivering at a field referral facility, then if the maximum TBA $\geq 10 < 20$, then cervical ripening or delivery can begin at 39 0/7. If the maximum TBA is ≥ 20 then the patient should be referred to ANMC at 37 0/7
4. Presumptive ICP patients, e. g., severe symptoms and normal labs, can receive cervical ripening or delivery at 39 0/7 in either a field setting or ANMC
5. Women with 'pruritus gravidarum' need not be scheduled for induction of labor/delivery at 39 weeks or receive antenatal testing if their symptoms remain mild. Deliver for usual obstetric indications.
6. Women with an unfavorable cervix are candidates for out-patient pre-induction cervical ripening with misoprostol if fetal surveillance is reassuring.
7. Please draw bile acids and LFTs on all four categories of patients upon admission to L/D.
8. Post-partum, hormonal contraception may be offered, as very few women will have recurrence of symptoms on such therapy.

Table 1			
History, symptoms, signs	Lab abnormalities*	Prior Treatment	Current Treatment
Mild ICP			
(Any one of these) <u>History</u> 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 <u>Exam</u> -observed scratching during clinical encounters -excoriations found on exam	(Any one of these) Maximum total bile acids > 10 umol/L < 40 Cholic acid > 3 umol/L Total Bilirubin > 1.0 mg/dL AST > 40 U/L ALT > 40 U/L Alk. phosphatase > 300 U/L *without hepatitis, steatosis, or cholelithiasis		Ursodiol starting at 15 mg/kg divided BID BPP q wk starting at 32 weeks Monitor TBA q wk starting at 36 wks Cervical ripening or cesarean delivery at 39 0/7 weeks
Severe ICP			
Maximum TBA \geq 40			Ursodiol starting at 15 mg/kg divided BID BPP q wk starting at 32 weeks Cervical ripening or cesarean delivery at 37 0/7 weeks
Presumptive ICP			
History of any one of the above signs, symptoms, or historical factors	None of the above	History of medical treatment, e. g., ursodiol during this pregnancy	Consider stopping ursodiol: -Repeat BAs q 2 wks

-Now or at any prior point in the current pregnancy			-BPP q wk starting at 32 weeks -if sx worsen, and/or repeat TBA are abnormal then perform cervical ripening or cesarean delivery at 39 0/7 weeks; -if sx minimal and repeat BA normal, diagnose as pruritus gravidarum
Pruritus gravidarum			
Pruritus, but non-severe	Normal Bile acids and LFTs 2 weeks apart		No antenatal testing Delivery for usual obstetric indications

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