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Review article

Intrahepatic cholestasis of pregnancy: Review of six national and regional guidelines

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ABSTRACT

Intrahepatic cholestasis of pregnancy (ICP) is a poorly understood disease of the late second or third trimester of pregnancy, typically associated with rapid resolution following delivery. It is characterized by pruritis, elevated serum bile acids, and abnormal liver function tests and has been linked to stillbirth, meconium passage, respiratory distress syndrome and fetal asphyxial events. The incidence is highly variable, dependent both on the ethnic makeup of the population as well as the diagnostic criteria being used. Management is challenging for clinicians, as laboratory abnormalities often lag behind clinical symptoms making diagnosis difficult. The American Congress of Gastroenterology, Government of Western Australia Department of Health, the Royal College of Obstetricians and Gynaecologists, Society for Maternal Fetal Medicine, European Association for the Study of the Liver, and South Australia Maternal and Neonatal Community of Practice have all released guidelines to address the risks, diagnosis and management of ICP. We performed a descriptive review of these guidelines along with a literature search to address conflicting recommendations and highlight new evidence. The variations in the guidelines reflect the heterogeneity of the literature and the challenges of diagnosing and managing ICP.

Contents

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Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a reversible cholestasis generally beginning in the second or third trimester characterized by pruritus with elevated serum bile acid concentrations and/or liver enzymes in the absence of other systemic or other hepatobiliary disorders [1–4]. ICP affects approximately 0.3–5.6% of pregnancies and has ethnic, geographic and seasonal variation [1,5–8]. The etiology is multifactorial and may be linked to increasing estrogen levels in pregnancy as well as altered expression of hepatobiliary transport proteins [3,9,10]. Adverse obstetrical outcomes include spontaneous preterm delivery, fetal asphyxia, and stillbirth [2,11–15]. Resolution is typically spontaneous following delivery; however, women with a history of ICP have an increased risk of developing hepatobiliary, immune-mediated, and cardiovascular diseases later in life [16,17]. Despite the associated adverse outcomes, opinions vary regarding appropriate diagnostic criteria, maternal and fetal surveillance, treatment, and delivery timing [18–23]. The relative infrequency of this condition, coupled with disparate guidelines, makes management decisions difficult for busy clinicians.

Aim

We sought to review the available English guidelines on ICP [18–23] and cull the evidence-based medicine to provide clinicians a clinically useful overview. Additionally, by discussing the variations in guidelines, we hope to highlight the importance of prospective clinical trials for ICP and promote the development of practice guidelines by other organizations.

Evidence acquisition

A search of published guidelines was performed on the websites of the American College of Gastroenterology (ACG) [24], American College of Obstetricians and Gynecologists (ACOG) [25], Royal Australian New Zealand College of Obstetricians and Gynaecologists [26], Royal College of Obstetricians and Gynaecologists (RCOG) [27], Society of Obstetricians and Gynaecologists of Canada [28], Royal College of Physicians of Ireland [29], and Society for Maternal Fetal Medicine (SMFM) [30] for ICP using the search terms “cholestasis”, “intrahepatic cholestasis”, and “jaundice of pregnancy”. Of these, ACG, RCOG and SMFM had independent guidelines on ICP: “Liver Disease in Pregnancy (2016)”, “Obstetric Cholestasis (2011)” and “Understanding Intrahepatic Cholestasis of Pregnancy (2011)”, respectively [18–20]. ACOG’s 2014 Clinical Expert Series article, “Intrahepatic Cholestasis of Pregnancy”, was not included as this was not considered a practice guideline [3]. PubMed and Internet searches were performed using the following terms: “intrahepatic cholestasis of pregnancy”, “obstetric cholestasis”, “cholestasis of pregnancy”, and “jaundice of pregnancy”. These searches yielded the European Association for the Study of the Liver (EASL) Clinical Practice Guideline “Management of Cholestatic Liver Diseases (2009)”, South Australia Maternal and Neonatal Community of Practice (SAMNCP) Clinical Guideline “Obstetric Cholestasis (2016)”, and the Government of Western Australia Department of Health (GWADOH) Clinical Guideline “Cholestasis in Pregnancy (2014)” [21–23].

The recommendations of ACG, EASL, GWADOH, RCOG, SAMNCP, and SMFM, including diagnostic criteria, laboratory testing, fetal risks, antepartum surveillance, medical management, delivery timing, and postpartum considerations, were summarized. The number of randomized control trials, systematic reviews and/or meta-analyses, and Cochrane reviews for each guideline were compared. Finally, a literature search was performed to help address conflicting recommendations and to highlight new evidence published after the release of these guidelines.

Discussion

Presentation of ICP

All six guidelines identify unrelenting pruritus without a rash, usually in the third trimester, as the primary presenting complaint of women with ICP [18–23]. Four of these guidelines elaborate on the pruritus, noting the tendency to involve the palms and soles, be worse at night, and possibly cause sleep disturbances (RCOG, GWADOH, SAMNCP, EASL) [19,21–23]. Patients may exhibit jaundice (ACG, RCOG, GWADOH, SAMNCP, EASL) [18,19–23] and 20% will have elevated direct bilirubin levels (SMFM) [20]. Steatorrhea may be present, though neither prevalence nor diagnostic criteria are discussed (RCOG, GWADOH, SAMNCP, EASL) [19–23]. More general complaints such as malaise and anorexia are mentioned only in the Australian guidelines (GWADOH, SAMNCP) [21,22].

RCOG, GWADOH, and SAMNCP all caution that the differential diagnosis of ICP include preeclampsia, hemolysis, elevated liver enzymes and low platelets syndrome (HELLP), and acute fatty liver of pregnancy [19,21,22]. Additionally, dermatologic conditions (pruritic urticarial papules and plaques of pregnancy, eczema, xerosis, pemphigoid gestations, allergic drug reactions) [19,21,22], liver disease (viral and autoimmune hepatitis, biliary tract obstruction, nonalcoholic steatohepatitis) [18,19,21,22], and substance abuse (drugs, alcohol) [22] need to be considered in the differential of ICP. All six guidelines recommend drawing bile acids and liver function tests, including transaminases and bilirubin, as a starting point [18,23].

Risk factors

A personal or family history of ICP is a risk factor in all six guidelines, and recurrence rates range from 40 to 92% [18–23]. ACG, RCOG, and SAMNCP identify cholelithiasis as a risk factor, but ACG notes that cholelithiasis may confound the diagnosis of ICP [18,19,22]. EASL and SMFM discuss multifetal gestation as a risk factor [20,23]. ACG, RCOG, and SMFM note patients who are seropositive for the hepatitis C virus may be at increased risk, though only SMFM cites an incidence (6–16%) [18,20]. All guidelines caution that viral hepatitis of any type should be considered when diagnosing ICP, especially in women with jaundice, steatorrhea, dark urine, or a history of illicit drug use [18–23].

Increased rates of ICP have been found in women with a range of hepatobiliary pathologies. Marschall et al. noted an increase in ICP

in women with prepregnancy hepatitis C (OR 5.76; 1.30–25.44), chronic hepatitis (8.66; 1.04–71.48), and cholelithiasis (OR 3.29; 2.02–5.36) in a Swedish retrospective cohort study from 2013 [16].

Multiple gene mutations have been identified helping to explain ethnic and familial clustering. Hepatobiliary transport proteins including the hepatic phospholipid transporter (MDR3/ABCB4), amninophospholipid transporter (ATP8B1/FIC1), and bile salt export pump (BSEP/ABCB11) have been implicated in familial ICP [9,31], and mutations in the nuclear hormone receptor farnesoid X have been described in a white European cohort [32].

Diagnosis

A lack of consensus in the diagnostic criteria contributes to the differences in management of ICP (Table 1) [18–23]. GWADOH and RCOG define ICP as obstetrical pruritus accompanied by otherwise unexplained elevation in liver function tests or bile acid concentrations, both of which resolve after delivery [19,21]. They go on to state that any value above the upper limit of normal for pregnancy of transaminases, gamma-glutamyl transpeptidase (γGT), or bile acid concentrations can be used [19,21]. RCOG specifically notes that elevated bile acid concentrations are not required for diagnosis [19]. ACG, EASL, and SMFM only mention persistent pruritus that resolves with delivery and bile acid concentrations > 10 μmol/L for diagnosis [18,20,23]. RCOG states that a confirmed diagnosis can only be made following resolution of symptoms and laboratory values postpartum [19], and all guidelines recommend reconsideration of an ICP diagnosis in the presence of persistent laboratory abnormalities following delivery [18–23].

SAMNCP is the only guideline to divide ICP into mild (bile acid concentrations 10–40 μmol/L) and severe (>40 μmol/L) forms. It notes that while bile acid concentrations >10 μmol/L are suggestive, values >15 μmol/L are diagnostic. It also excludes elevated transaminases from the diagnostic criteria [22].

Antepartum care

Following diagnosis of ICP, the recommended management varies between all six guidelines (Table 2) [18–23]. GWADOH, RCOG, and SAMNCP all recommend drawing weekly liver function tests to monitor disease progression, as more severe biochemical abnormalities may warrant earlier delivery [19,21,22]. Only SAMNCP defines these abnormalities (Table 2) 22]. Coagulation tests are also recommended either before labor (SAMNCP) [22], or if liver function tests are abnormal (RCOG, GWADOH) [19,21]. Laboratory testing for other etiologies of elevated liver function tests, such as viral hepatitis, Epstein Barr virus, cytomegalovirus, primary biliary cirrhosis, and primary sclerosing cholangitis should be tailored to individual risk facstors as shown in Table 3 (RCOG, GWADOH, SAMNCP) [19,21,22,33–39]. Both ACG and GWADOH recommend ultrasound to exclude obstructive hepatobiliary disease [18,21]. EASL recommends repeating alanine transaminase (ALT), bilirubin, γGT, bile acid concentrations, and prothrombin time if the values were normal on presentation but pruritus is persistent [23]. SMFM only recommends considering hepatitis C screening [20].

For bile acid concentrations > 40 μmol/L or ALT > 200 IU/L, which encompasses 17–30% of ICP women [40–42], SAMNCP recommends inpatient management [22]. They recommend that bile acid concentrations and liver function tests be drawn twice weekly, and coagulation tests be performed at the time of diagnosis of severe disease and again prior to labor. They do not provide recommendations regarding fetal monitoring while admitted. If medications lower ALT or bile acid concentrations below threshold values, they state outpatient management is again acceptable and labs may be drawn weekly [22].

Antenatal testing

Antenatal testing in women with ICP has not been proven to be effective in predicting pregnancies at risk of fetal death [15,43,44] and is currently recommended only by SMFM [20]. SMFM states that while antepartum fetal testing is recommended, it cautions that the appropriate type, duration, or frequency of testing has not been identified and the recommendation is not evidence based [20]. Notably, ACOG does not include ICP among its indications for antenatal testing [45]. RCOG notes that cardiotocography, ultrasound, and fetal kick counts have been considered but efficacy data are lacking [19]. Monitoring umbilical artery (UA) Doppler velocimetry is discussed but not formally recommended by RCOG given there are no differences from normal pregnancy [19,46]. SAMNCP cautions that normal fetal heart tracings and fetal activity have been documented hours before stillbirth [22]. ACG and EASL do not discuss antenatal testing [18,23]. If antenatal testing is performed for women with ICP, they should be made aware of the limitations of such testing in predicting adverse perinatal outcomes (RCOG) [19].

Antepartum medical treatment

Ursodeoxycholic acid (UDCA)

UDCA is recommended as first line treatment in all six guidelines [18–23] and has been shown to reduce maternal pruritus as well as decrease laboratory abnormalities [5,40,47–50]. ACG is the only organization to suggest there may be fetal benefit associated with its use [18]. Both ACG and GWADOH recommend

Table 1
Comparison of diagnostic criteria for ICP from guidelines.

Variable	RCOG	SAMNCP	GWADOH	ACG	EASL	SMFM
Pruritus	Required	Required	Required	Required	Required	Required
γGT	Diagnostic if ↑	Not diagnostic	Diagnostic if ↑		Not diagnostic	
Bile acid	Diagnostic if ↑; not required	Required for diagnosis; >10 IU/L suggestive; >15 IU/L diagnostic; >40 IU/L severe	Diagnostic if ↑; not required	>10 IU/L is diagnostic		
Transaminases	Diagnostic if ↑	May be ↑	Diagnostic if ↑	May be ↑	May be ↑	May be ↑
Resolution after delivery	LFTs decline after 10 days, resolve in 6 wks	Pruritus: 1-2 days Jaundice: 1 wk Bile acid: 1 wk LFTs: 6 wks	Pruritus: 1-2 days LFTs: 1 month	YES		Pruritus: days

Abbreviations - ACG American College of Gastroenterologists; EASL European Association for the Study of the Liver; GWADOH Government of Western Australia Department of Health; γGT gamma-glutamyl transpeptidase; LFTs liver function tests; RCOG Royal College of Obstetricians and Gynaecologists; SAMNCP South Australia Maternal and Neonatal Community of Practice; SMFM The Society for Maternal-Fetal Medicine.

Table 2
Summary of management recommendations of ICP from guidelines.

Variable	RCOG	SAMNCP	GWADOH	ACG	EASL	SMFM
Laboratory Evaluation						
Bile acids	YES	YES	YES	YES	YES	YES
Fasting bile acids			YES			
LFTs	YES	YES	YES	YES	YES	YES
γGT	YES	YES	OPTIONAL		YES	
PT					YES	
Subsequent Antenatal Evaluation	Weekly LFTs, PT/PTT if LFTs rapidly escalate	Weekly bile acids and LFTs (twice weekly if severe disease)	Weekly LFTs, PT/PTT if abnormal LFTs	US to rule out cholecystitis	Repeat initial workup if normal but pruritus persistent	
Antepartum Care						
Antenatal Testing			At discretion of obstetric team			YES
Prenatal visits			Every 2 wks			
Delivery Timing	37 wks	38 wks if severe disease; earlier if bile acids >100 μmol/L)	37–38 wks; earlier if maternal or fetal compromise	37 wks	36-38 wks	37-38 wks; sooner with documented pulmonary maturity
Intrapartum care						
Continuous FHR monitoring	YES		YES			
Active management of third stage		YES				
Admission labs		PT/PTT	Crossmatch CBC CMP PT/PTT if LFTs abnormal			
Other			NICU if meconium suspected			
Medical Management						
UDCA	No dosing provided	•Starting dose: 250 mg TID •Maximum dose: 750 mg 3-4 times per day	10-15 mg/kg/day	10-15 mg/kg/day	•Starting dose: 10–20 mg/kg/day •Maximum dose: 25 mg/kg/day	•Starting dose: 300 mg BID •Maximum dose: 600 mg BID
Vitamin K (maternal)	YES (5-10 mg/day if prolonged PT)	YES (10 mg/day if prolonged PT)	YES (5-10 mg/day PO)		YES (if prolonged PT)	
Dexamethasone	Not for first line use			May be used to promote fetal lung maturity	May be used for pruritus	
S-adenosyl methionine					May be combined with UDCA	
Rifampicin		Consider if UDCA fails			Consider if UDCA fails	
Postpartum Care						
Hormonal contraception	NO					OK
Breastfeeding						OK
Repeat LFTs	6 wks	1 month (with bile acid)	2-4 wks	Evaluate other etiologies if symptoms persist	Evaluate other etiologies if symptoms persist	

Abbreviations - ACG, American College of Gastroenterologists; CBC, complete blood count; CMP, complete metabolic panel; EASL, European Association for the Study of the Liver; FHR, fetal heart rate; GWADOH, Government of Western Australia Department of Health; γGT, gamma-glutamyl transpeptidase; LFT, liver function tests; PT, prothrombin time; PTT, partial prothrombin time; RCOG, Royal College of Obstetricians and Gynaecologists; SAMNCP, South Australia Maternal and Neonatal Community of Practice; SMFM, The Society for Maternal-Fetal Medicine; UDCA, Ursodeoxycholic acid.

10–15 mg/kg/day [18,21], while SAMNCP recommends starting at 250 mg three times per day for mild disease, 500 mg three times per day for severe disease, up to a maximum of 750 mg three to four times per day [22]. EASL recommends 10–20 mg/kg/day, with a maximum dose of 25 mg/kg/day [23]. SMFM dosing starts at 300 mg twice daily, increasing to 600 mg twice daily if symptoms do not improve in one week [20]. RCOG does not provide recommendations on dosing [19].

Vitamin K

Vitamin K supplementation is recommended by all guidelines except ACG and SMFM [19,21–23]. Both RCOG and SAMNCP recommend starting Vitamin K at 5–10 mg per day if there is an elevated prothrombin time (PT) [19,22], while GWADOH recommends treatment for all patients with ICP to prevent postpartum hemorrhage [21]. EASL agrees with supplementation when the PT is prolonged, but does not provide dosing [23]. There is limited evidence to support the prophylactic use of Vitamin K in the absence of prolonged PT, and a recent retrospective study showed no correlation between postpartum blood loss and ICP, regardless of disease severity [41].

Dexamethasone

Dexamethasone is recommended by ACG and EASL only to promote fetal lung maturity [18,23]. RCOG cautions that dexamethasone should not be considered for first line maternal treatment due to insufficient data and potential for adverse neonatal neurologic outcomes [19]. SMFM states that corticosteroids can be used for pruritis, but they are not superior to UDCA [20]. Neither GWADOH nor SAMNCP discuss the use of corticosteroids [21,22]. A 2005 randomized clinical trial concluded that dexamethasone provided no reduction in pruritis, fetal

Table 3
Confounding diseases.

Disease	Risk Factors	Suggested Testing
Hepatitis A virus [33,34]	Recent travel to developing countries Exposure to children attending daycare Oral-anal contact Illicit drug use History of clotting disorders	Hepatitis A IgM
Hepatitis B virus [33,34]	Born in or recently travelled to Asia, Africa, Middle East, Eastern Europe, South America, Central America or the Caribbean Injection drug use Immunosuppressed, including HIV, cancer, or use of immunomodulating agents Receive hemodialysis Exposure to infected persons in household Multiple sexual partners	Hepatitis B surface antigen
Hepatitis C virus [33,34]	Injection drug use Received clotting factors prior to 1987 Received blood transfusion or donated organs prior to 1992 Receive hemodialysis Infected with HIV History of tattoos or body piercings with non-sterile instruments Born to mother with hepatitis C	Hepatitis C antibody
Autoimmune hepatitis [35]	Autoimmune processes including celiac disease, Crohn's disease, ulcerative colitis, Grave's disease, Hashimoto's thyroiditis, Sjogren's syndrome, systemic lupus erythematous, rheumatoid arthritis, and type 1 diabetes	Anti-nuclear antibody Anti-smooth muscle antibody Anti-liver/kidney microsomal antibody
Epstein Barr virus [36]	Recent fever, fatigue, or inflamed throat Enlarged spleen or liver on exam Exchange of bodily fluids with infected person	Anti-viral capsid antigen IgM
Cytomegalovirus (CMV) [37]	Signs or symptoms of Epstein Barr virus or viral hepatitis but with negative viral testing for both	CMV IgM, and CMV IgG avidity testing
Primary biliary cirrhosis [38]	Severe fatigue, possibly associated with daytime somnolence Sicca Syndrome, scleroderma, rheumatoid arthritis, or Raynaud phenomenon	Anti-mitochondrial antibody
Primary sclerosing cholangitis [39]	Jaundice and/or hepatosplenomegaly Inflammatory bowel disease	Magnetic resonance cholangiography

complication rates, or ALT levels and was less effective than UDCA at reducing serum bile acids and bilirubin [40].

Other treatment options

GWADOH, RCOG, SAMNCP, and SMFM all discuss over-the-counter medications such as aqueous cream with menthol, lotions, or anti-histamines as safe methods to relieve pruritus [19–22]. RCOG discusses that heparin, rifampicin, and nor-UDCA are currently under investigation [19]. SMFM states that *S*-adenosylmethionine can be used with UDCA to decrease bile acids and transaminases, but does not provide dosing recommendations [20]. EASL notes that rifampicin and *S*-adenosylmethionine may have some additive effect when combined with UDCA, but these drugs should be considered on an individualized basis [23].

A 2013 Cochrane Review concluded that there was insufficient evidence to indicate that S-adenosylmethionine, guar gum, activated charcoal, dexamethasone, cholestyramine, Salvia, Yinchenghao decoction, Danxioling and Yiganling, or Yiganling alone are effective in treating women with ICP [49].

Delivery timing

Early term induction is discussed in all guidelines [18–23]. ACG recommends delivery at 37 weeks [18]. RCOG advises discussing with patients the option of early term delivery versus expectant management [19]. RCOG notes that induction may be preferential in pregnancies with more severe laboratory abnormalities but does not define these laboratory values [19]. SAMNCP advises delivery at 38 weeks for severe disease and to consider earlier induction of labor if bile acid concentrations are >100 μmol/L [22]. GWADOH recommends delivery between 37 and 38 weeks unless maternal or fetal compromise dictates earlier induction [21]. It should be noted that while ACOG does not have a formal guideline for ICP, a separate guideline supports ICP as an indication for late-preterm or early-term delivery [51]. SMFM states that while an evidence-based recommendation is not available for the timing of delivery, most strategies advocate for delivery between 37–38 weeks or sooner with documented pulmonary maturity [20]. Additionally, they state that prior obstetrical history, antenatal testing, and gestational age should be considered [20]. EASL notes that delivery between 36–38 weeks appears to prevent stillbirth, but it is not evidence-based [23].

A 2014 decision-analytic model determined the optimal age for delivery in patients with ICP to be 36 weeks. This was based on 18 published studies and assumption of a uniform rate of stillbirth of 1.74% [52]. A 2015 retrospective cohort study supported these findings and concluded delivery at 36 weeks, or at the time of diagnosis if beyond 36 weeks, would minimize mortality risk [53]. In contrast, a 2014 systematic review of 16 articles from 1967 to 2011 concluded that the risk of fetal death is clinically insignificant and without statistical proof; therefore, early delivery is inappropriate [4]. Finally, a randomized clinical trial in 2012 compared UDCA versus placebo and early term delivery versus expectant management. There was no significant difference between early term delivery versus expectant management, and the authors concluded that the sample size needed to appropriately power such a study may not be feasible [50]. There are no published randomized control trials that are sufficiently powered to compare delivery outcomes at different gestational ages, regardless of disease severity, for the prevention of perinatal morbidity or mortality.

Delivery management

SAMNCP and GWADOH advise checking coagulation tests at the time of admission if there is severe disease or if liver function tests

are abnormal on admission [21,22]. SAMNCP recommends active management of the third stage of labor [22]. In addition to coagulation tests, GWADOH advises a complete blood count and crossmatched blood be ordered [21]. They recommend the presence of neonatology at delivery if meconium is suspected [21]. Both GWADOH and RCOG support the use of continuous fetal heart monitoring [19,21]. ACG, EASL, and SMFM do not offer specific guidance regarding delivery management [18,20,23].

Postpartum care

GWADOH, RCOG, and SAMNCP all recommend repeating liver function tests in two to six weeks after delivery [19,21,22]. RCOG suggests drawing liver function tests at six weeks followed by an additional postpartum visit at eight weeks [19]. Repeating bile acid concentrations is recommended only by SAMNCP [20]. EASL suggests that if the laboratory abnormalities do not normalize postpartum, primary biliary cirrhosis, primary sclerosing cholangitis, or chronic hepatitis C should be considered [23]. SMFM notes that pruritus usually resolves within days of delivery [20]. Breastfeeding is not contraindicated after a diagnosis of ICP (SMFM) [20].

Contraceptive counseling

Estrogen containing birth control is generally avoided per RCOG guidelines [19]. GWADOH recommends against combined oral contraceptive pills but states low dose estrogens or progesterone-only pills are recommended [21]. SMFM states hormonal contraception is not contraindicated in pregnancies complicated by ICP [20]. ACG, EASL and SAMNCP do not address postpartum contraception [18,22,23], but EASL notes high dose oral contraceptive pills and progesterone can trigger ICP [23]. It should be noted that the Center for Disease Control United States Medical Eligibility Criteria for Contraceptive Use states that all contraceptive options are a considered Category 1 while estrogen containing contraceptive options are considered Category 2 (i.e. advantages generally outweigh theoretical or proven risks) [54].

Future risk

RCOG recommends discussing the risk of recurrence (45–90%) with patients at the time of the postpartum evaluation [19]. SMFM states the recurrence risk is 50–60% but may be as high as 92% in familial cases [20]. GWADOH and SAMNCP both cite a recurrence risk of 40–60% [21,22]. Neither ACG nor EASL discuss recurrence risk in their respective guidelines [18,23].

GWADOH and SAMNCP both caution that women with severe familial forms of ICP are at increased risk for chronic liver disease later in life [21,22]. Marschall et al. found these risks extend beyond the known familial forms [16]. Their 2013 population-based cohort study examined 11,388 Swedish women with ICP and linked them to future development of hepatobiliary diseases through their nationwide patient registry. Compared to healthy controls, women with a history of ICP had increased rates of hepatitis C (HR 4.16; CI 2.47–2.77), chronic hepatitis (HR 5.96; CI 3.43–10.33), cirrhosis (HR 5.11; 3.29–7.96), gallstones disease (HR 2.72; 2.55–2.91), or cholangitis (4.22; 3.13–5.69) [16]. A 2015 study using the same database found increased risks of hepatobiliary cancer, cardiovascular disease, and immune-mediated diseases including diabetes mellitus, thyroid disease, psoriasis, inflammatory polyarthropathies, and Crohn's disease [17].

Conclusion

ICP is a challenging condition to manage given the paucity of high quality studies (Table 4). While several organizations agree on the clinical presentation of ICP, few agree on diagnostic criteria. Without established criteria, prevalence data varies widely and interpretation of studies is confounded. These inconsistencies make recommendations difficult, perhaps explaining the disparities in the reviewed guidelines.

Of the six guidelines found for review, only RCOG and SMFM are internationally recognized for obstetrical care. ACG and EASL provide advice derived from expertise in hepatology, but the recommendations are appropriately narrow in scope. State and regional recommendations (e.g. GWADOH and SAMNCP) provide guidance where national guidelines are unavailable. In Australia and New Zealand, a survey of physicians on management of ICP found that 39% use RCOG guidelines, 24% use state and local recommendations, and 37% did not use any guidelines [55].

The lack of consensus guidelines and inconsistent data in the literature has led to varied practices in the management of ICP, even in countries with established recommendations. Despite RCOG guidelines discussing the absence of data to support UA Doppler velocimetry and fetal growth assessment in ICP [19], 77% of British obstetricians monitor UA Doppler velocimetry and 82% perform ultrasound examinations to evaluate fetal growth [56]. Several recent studies involving women in Sweden, the United States, and the United Kingdom have called attention to an associated between gestational diabetes, large for gestational age infants, and ICP [17,57]. So, while growth ultrasounds are not currently recommended, it is important physicians remain congnescent of these potential risks and screen appropriately for gestational diabetes and fetal growth abnormalities.

The strengths of this analysis include synthesizing the recommendations of six different organizations and analyzing

Table 4
Comparison of references from guidelines.

Variable	RCOG (2011)	SAMNCP (2016)	GWADOH (2014)	ACG (2016)	EASL (2009)	SMFM (2011)
Total references	76	20	15	13	16	19
Common references*	11	9	6	6	12	13
Obstetrical references	43	8	5	4	7	13
Gastrointestinal/ hepatobiliary references	16	6	4	6	8	5
Years published	1963–2011	1997–2015	2004–2013	1978–2013	1997–2008	1986–2008
Randomized trials cited	11	4	0	0	5	5
Cochrane Reviews cited	1	1	1	0	0	1
Systematic reviews or meta-analyses cited	2	2	4	1	0	1

Abbreviations - ACG, American College of Gastroenterologists; EASL, European Association for the Study of the Liver; GWADOH, Government of Western Australia Department of Health; RCOG, Royal College of Obstetricians and Gynaecologists; SAMNCP, South Australia Maternal and Neonatal Community of Practice; SMFM, The Society for Maternal-Fetal Medicine.
*Reference is shared with at least one other guideline.

their perspectives on the clinical features, risk factors, diagnosis, antepartum management, medical treatment, and postpartum care of women with ICP. A major limitation of this study was limiting the review to English guidelines. The Czech Republic, Poland, and China have published on the topic [58–61], and a search in their respective languages was not performed. We also recognize that, while not the intention of this study, this review did not contribute to the available data on ICP.

In closing, ICP remains a potentially dangerous and poorly understood condition with diagnostic and management questions yet to be answered. In particular, the underlying pathophysiology of the adverse pregnancy outcomes in ICP is poorly understood. A large, multicenter, prospective cohort study evaluating the association between bile acids and adverse perinatal outcomes and identifying optimal delivery timing is needed. Unfortunately, an adequately powered study to evaluate these questions is unlikely given ICP and its associated perinatal morbidity and mortality are rare. As more data become available, the emergence and coalescence of new guidelines should standardize care and improve patient outcomes.

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