Total serum bile acids or serum bile acid profile, or both, for the diagnosis of intrahepatic cholestasis of pregnancy

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Total serum bile acids or serum bile acid profile, or both, for the diagnosis of intrahepatic cholestasis of pregnancy (Protocol)

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[Diagnostic Test Accuracy Protocol]

Total serum bile acids or serum bile acid profile, or both, for the diagnosis of intrahepatic cholestasis of pregnancy

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ABSTRACT

This is a protocol for a Cochrane Review (Diagnostic test accuracy). The objectives are as follows:

To determine the diagnostic accuracy of total serum bile acids or total serum bile acids profile, or both for the diagnosis of intrahepatic cholestasis of pregnancy in pregnant women presenting with pruritus.

To compare the diagnostic accuracy of total serum bile acids and each component of serum bile acid profile, considered independently or in combination, in diagnosing intrahepatic cholestasis of pregnancy; to define the optimal cut-off values for these; and to investigate possible sources of heterogeneity.

BACKGROUND

Intrahepatic cholestasis of pregnancy (also known as obstetric cholestasis) is a pregnancy-specific liver disorder, that is possibly associated with an increased risk of severe fetal adverse events. Intrahepatic cholestasis of pregnancy was first described in 1883 (Ahlfeld 1883), and many other publications have followed. However, our knowledge of the disease is still incomplete (Reyes 1997; Sinakos 2010).

The prevalence of intrahepatic cholestasis of pregnancy varies according to geographical location and ethnicity, as genetic and environmental factors play a role in its manifestation (Geenes 2009). The range of intrahepatic cholestasis of pregnancy has been calculated to be between 0.01% and 0.1% in North America, Southern Europe, Asia, and Australia (Reyes 1997); between 1.5% and 4.0% in South America (Reyes 1997); and 1.5% in Scandinavia (Glantz 2004). Among the most affected countries in the world

are Chile, Bolivia, Finland, Sweden, and Portugal (Geenes 2009).

Most often the disease affects women with a history of intrahepatic cholestasis during previous pregnancies (Reyes 1997), history of cholestasis associated with the use of oral contraceptives (Pathak 2010), family or personal history of biliary disease (Diken 2014), hepatitis C viral infection (Paternoster 2002), twin pregnancies (Gonzalez 1989), or in vitro fertilisation pregnancies (Koivurova 2002). It is also suggested that the risk of acquiring intrahepatic cholestasis of pregnancy is higher in women over the age of 35 years (Heinonen 1999).

There are multiple factors involved in the aetiopathogenesis of intrahepatic cholestasis of pregnancy. Among the genetic factors suspected in causing the disease are mutations in genes that encode biliary transport proteins (Dixon 2014), or mutations in bile acid receptors (such as farnesoid X receptor (Jacquemin 1999)). Likewise, among factors suspected in causing the disease are seasonal variations (with higher prevalences reported in winter (Brites 1998a)), low selenium intake, erucic acid, increased gut absorption of bacterial endotoxins, pollutants (such as pesticides), infections, or drugs (Geenes 2009; Diken 2014; Ozkan 2015). Hormonal factors such as oestrogens, progesterone, or their metabolites can also play a role in its development (Reyes 2008; Abu-Hayyeh 2013). Seasonal variations and an increase in dietary selenium intake may have played a role in the decrease of the prevalence of the disease observed in Chile and Scandinavia since the late 1980s' (Kauppila 1987; Reyes 2000a). Probably owing to these variations, the prevalence of intrahepatic cholestasis of pregnancy in Chile decreased from a range of 11.8% to 27.7% during the 1970s (the higher value observed for Araucanian ethnicity) (Reyes 1978) to the most recently reported range of 1.5% to 4.0% in the 1990s (Reyes 1997).

Some studies showed an association between intrahepatic cholestasis of pregnancy and metabolic abnormalities in affected pregnant women, such as impaired glucose tolerance, hyperinsulinaemia, or dyslipidaemia (Martineau 2015), which may lead to increased fetal growth and sex-specific increased susceptibility to an obese, diabetic phenotype of the offspring (Desai 2013; Papacleovoulou 2013).

In clinical practice, presence of pruritus from the last third of pregnancy and the 'otherwise unexplained' abnormalities in the most common liver tests, seems enough to support the diagnosis of intrahepatic cholestasis of pregnancy (Green-top Guideline no.43). However, owing to the non-specific features of the disease, the mandatory exclusion of all other possible underlying diseases is not always easy and to ascertain the right diagnosis may not be possible until a certain time point after the delivery, when the spontaneous relief of pruritus and normalisation of liver test values occur (Beuers 2006).

The pathophysiology of intrahepatic cholestasis of pregnancy is still poorly understood. An increase in bile acid serum concentration is thought to play a primary role in the onset of the typical cholestatic pruritus (Pathak 2010); however, a correlation between the bile acid serum concentration and severity of pruritus has not been demonstrated. Moreover, the increased passage of bile acids through the placental barrier appears to be toxic for the fetus during intrahepatic cholestasis of pregnancy (Perez 2005; Sheik Abdul Kadir 2010). Therapies so far have been empirical, and they all aimed at reducing maternal symptoms, improving results of liver tests, and reducing total bile acid concentration. Ursodeoxycholic acid (UDCA), S-adenosylmethionine (SAMe), dexamethasone, or cholestyramine as well as vitamin K (aiming at preventing possible postpartum bleeding) are the most used therapies (Ozkan 2015). To try to reduce the risk of stillbirth, which seems to occur most often in the last weeks of pregnancy (Puljic 2015), most clinicians choose an early delivery of the baby because of the medical condition of the mother, usually at week 37. Whether the increased preterm birth rate associated with intrahepatic cholestasis of pregnancy is due to the disease itself or to its active management is still uncertain (Henderson 2014).

One Cochrane Review on interventions for treating cholestasis in pregnancy concluded that there was no evidence to recommend early-term delivery and that there was insufficient evidence to support the use of SAMe, guar gum, activated charcoal, dexamethasone, cholestyramine, yinchenghao decoction, danxiaoling pill, yiganling, alone, or in combination (Gurung 2013). However, the review found that UDCA seemed to improve the maternal symptom of pruritus (Gurung 2013), which agrees with the result of a meta-analysis by Bacq and colleagues published in 2012 (Bacq 2012). In addition, the meta-analysis by Bacq strongly suggested that UDCA was also beneficial for the fetal outcome (Bacq 2012); however, the Cochrane Review did not reach this conclusion as the evidence was insufficient (Gurung 2013).

Total serum bile acids (TSBA), alone or in combination with serum aminotransferases, are the most often used biomarkers for intrahepatic cholestasis of pregnancy in clinical practice. Some components of the serum bile acid profile, especially primary bile acid concentrations (Sjövall 1966; Laatikainen 1977; Heikkinen 1983) or total concentration of tauro-conjugated (T-c) forms (Tribe 2010), may provide more specific information than TSBAs when diagnosing the disease, defining its severity, and monitoring its response to treatment (Chen 2013).

Target condition being diagnosed

Intrahepatic cholestasis of pregnancy is a gestation-specific liver disorder, defined most often as onset of pruritus, usually from the third trimester of pregnancy, associated with abnormal liver test results or raised TSBA, or both, and spontaneous relief after delivery in the absence of other skin or liver diseases. Severe intrahepatic cholestasis of pregnancy (defined by most authors when TSBA are greater than 40 µmol/L) (Glantz 2004) seems to be

associated with an increased proportion of serious adverse fetal outcomes which include fetal distress, sudden intrauterine death (possibly due to an acute anoxic event (Sepúlveda 1991) or impaired fetal cardiomyocyte function (Williamson 2001)), preterm labour, meconium staining of amniotic fluid, low birth weight, or respiratory distress syndrome of the baby (Glantz 2004; Zecca 2006). However, one systematic review restricted to English language literature published in 2014 found that the increased risk for stillbirth, associated most often with intrahepatic cholestasis of pregnancy, might be questionable because of the scant information on how the attributable risk associated with the disease had been calculated (Henderson 2014).

Clinical suspicion of intrahepatic cholestasis of pregnancy usually begins from the third trimester with an onset of mild-to-severe pruritus, frequently generalised on the palms and soles, getting worse at night and with advancing gestation (Kenyon 2001). In severe cases, it can also affect the ears, the eyelids, and even the oral cavity (Reyes 1997). Pruritus in the absence of skin rash, with the exception of scratching excoriations, could be the only presenting symptom of the disease, while constitutional symptoms (insomnia, fatigue, anorexia, malaise, or abdominal pain) or typical cholestatic symptoms (jaundice, malabsorption and vitamin K deficiency, steatorrhoea, pale stools, or dark urine) are rare (Hepburn 2008; Kondrackiene 2008; Mays 2010). Some studies describe instances of pruritus from earlier stages of pregnancy (Brites 1998b; Keitel 2006; Hubschmann 2016).

Onset of pruritus in late pregnancy usually directs clinicians to perform liver function tests, and rule out other possible diseases with serum or urinary markers, and imaging techniques. Despite the many available tests, an accurate and early diagnosis of intrahepatic cholestasis of pregnancy can be difficult, as it shares some of its clinical features and laboratory findings with other skin diseases (e.g. stretch marks of pregnancy; eczema; pruritic urticarial papules and plaques of pregnancy; infectious, allergic, or immunological skin disorders, etc.); liver diseases (e.g. viral and autoimmune hepatitis, tumours of hepatobiliary tract, bile stones of the biliary tree, etc.) (Diken 2014); conditions which may lead to icterus (e.g. severe hypoglycaemia, some types of encephalopathy, disseminated intravascular coagulation, etc.); obstetric-specific benign diseases (e.g. pruritus gravidarum, defined as idiopathic onset of pruritus during pregnancy but with normal liver tests, or asymptomatic hypercholanaemia of pregnancy, defined as serum bile acids level above the upper normal limit without symptoms) (Castaño 2006); or also more serious diseases (e.g. pre-eclampsia, haemolysis-elevated liver enzymes-low platelet count syndrome, or acute fatty liver disease) (Bacq 2011).

Even if most clinicians, in the least suspicion of the disease, initiate an empiric treatment with UDCA, prophylactic vitamin K, or antihistaminics (or also dexamethasone if pruritus is unbearable), the diagnosis can only be confirmed when the spontaneous relief of symptoms and signs after delivery occurs within the usual 48 hours or a few weeks later (two to four weeks), or at most eight weeks (Geenes 2009). In extremely rare occasions, women may have symptoms for longer periods of time (Olsson 1993; Aytaç 2006). If the symptoms or signs, related to suspected intrahepatic cholestasis of pregnancy, do not disappear within one month, clinicians should consider other differential diagnosis; and further investigations are mandatory (Bacq 2011).

Index test(s)

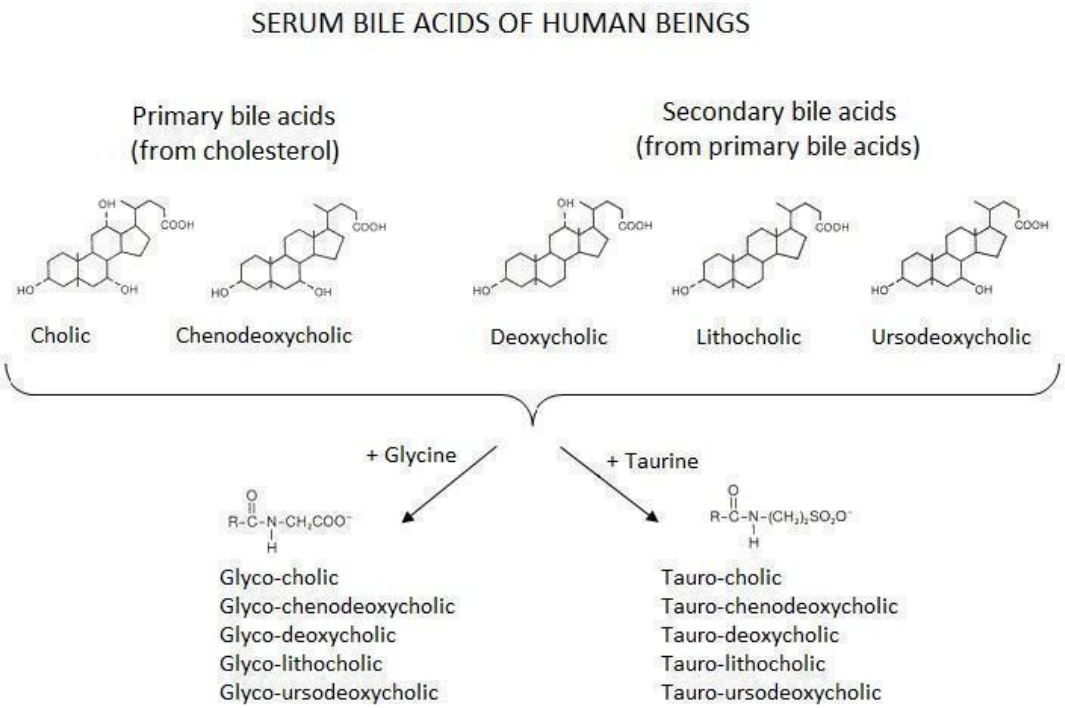
Total serum bile acids

The most frequently used cut-off value of TSBA concentration for the diagnosis of intrahepatic cholestasis of pregnancy is around 10 µmol/L to 14 µmol/L (Diken 2014). However, there is a variability in the cut-off values provided in the literature because of the method of measurement, fasting status, population studied, or gestational age at diagnosis (Pathak 2010). In addition, an early finding of normal levels of bile salts during the course of the disease does not exclude the diagnosis of intrahepatic cholestasis of pregnancy, and isolated elevation of bile salts in asymptomatic pregnant women may occur. However, this finding is uncommon and is most probably asymptomatic hypercholanaemia of pregnancy (Castaño 2006). Therefore, the high diagnostic accuracy attributed to TSBAs for intrahepatic cholestasis of pregnancy is questionable (Brites 1998a; Diken 2014).

Serum bile acid profile

The serum bile acid profile is composed of concentrations of individual primary bile acids (cholic acid (CA) and chenodeoxycholic acid (CDCA)), secondary bile acids (deoxycholic acid (DCA), lithocholic acid (LCA), UDCA), and their individual or total glyco-conjugated (G-c) and T-c forms (Figure 1), including ratios of some of them (CA/CDCA, total G-c/total T-c), measured in micromoles per litre. As the measurement of the individual components of the serum bile acid profile for the diagnosis of intrahepatic cholestasis of pregnancy has never been introduced in clinical practice, universally accepted cut-off values have not been determined.

Figure 1.



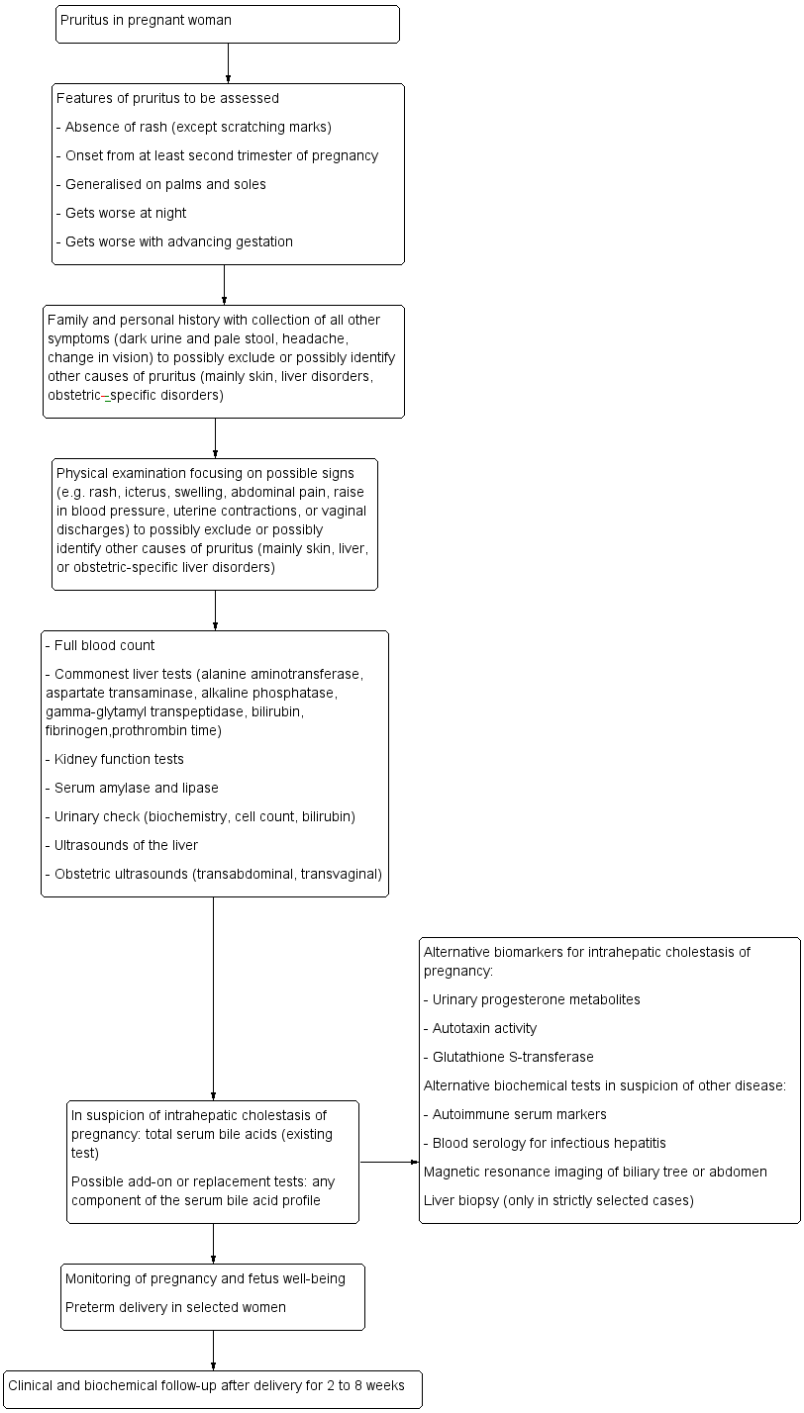
The currently available laboratory methods for bile acid analysis are enzyme assay; radioimmunoassay; enzyme immunoassay; and chromatographic methods such as thin-layer chromatography, gas chromatography, high-performance liquid chromatography, supercritical fluid chromatography, and capillary electrophoresis, coupled with mass spectrometry, fluorometry, ultraviolet detection, or electrochemical detection methods. Therefore, we expect to have heterogeneous results depending on the method used.

Clinical pathway

We describe the current clinical pathway for the diagnosis of intrahepatic cholestasis of pregnancy following the 'Green-top Guideline no.43' published by Royal College of Obstetricians and Gynaecologists (Green-top Guideline no.43).

Figure 2 presents a schematic overview of the current clinical pathway.

Figure 2. Clinical diagnostic pathway for the diagnosis of intrahepatic cholestasis of pregnancy.



Prior test(s)

Clinical suspicion of intrahepatic cholestasis of pregnancy usually arises when a woman arrives at a clinical setting claiming onset of pruritus in the second or third trimester of pregnancy. Initial examination is to assess the pruritus thoroughly; does it fit within the description of intrahepatic cholestasis of pregnancy or not?
The clinician should collect data on the woman's personal and family history to exclude all other possible causes of pruritus or a liver disorder, and to identify the possible risk conditions for infectious diseases or cholestasis. The focus should be on possible previous known or unknown skin conditions; acute or chronic liver diseases of any aetiology; pregnancy-specific disorders; family, personal, and obstetric history; drug history; and travel or meals at risk of exposure to infective agents. The clinician should determine if the woman has recently had changes in vision, headache, fever, abdominal pain, uterine contractions, or if she has noticed dark urine and pale stool, or vaginal discharges of any type.
Through physical examination, the clinician should be able to provide further information to rule in or rule out all possible differential diagnoses, attesting if any types of rash, icterus, swelling, hepatosplenomegaly, abdominal pain, uterine contractions, and hypertension are present. Then, the clinician may strengthen their diagnostic suspicion by ordering full blood count tests, serum liver function or liver biochemistry tests, serum pancreatic amylase and lipase, kidney function tests, or urinary check.
Liver biochemistry or liver function tests are commonly performed when intrahepatic cholestasis of pregnancy is suspected, but their normal upper limits in pregnant women are still under discussion (Mullally 2002). Among the most common liver tests are serum aminotransferases (altered in up to 60% of women, but with lower values compared to other aetiologies of liver disease such as viral hepatitis) (Diken 2014); gamma-glutamyl transpeptidase (raised in less than one-third of women) (Floreani 2006); alkaline phosphatases (not so reliable during pregnancy as its placental synthesis leads to physiologically increased values (Bacq 1996)); serum or urinary total, conjugated, and unconjugated bilirubin (raised in about 25% of women, but with lower values compared to other cholestatic diseases) (Reyes 1992); and fibrinogen and prothrombin time. Prothrombin levels can be altered with severe liver dysfunction or vitamin K malabsorption due to cholestasis, leading to an increased risk of postpartum bleeding, but this is very rare in intrahepatic cholestasis of pregnancy (Reyes 1992). Some women will have pruritus for days or weeks before the development of abnormal liver tests. In pregnant women with persistent unexplained pruritus, liver tests should be performed every week or two. If clinical evidence and liver tests show a pattern consistent with a viral or autoimmune aetiology (e.g. high elevation of serum aminotransferases), further testing is needed (Green-top Guideline no.43).
Ultrasound examination of the liver and biliary tract could help to rule out other causes of liver disease or of cholestasis, especially extrahepatic cholestasis (e.g. stones or tumours of the biliary tree) (Boregowda 2013).
Obstetric examination with ultrasound scans could help to rule out high-risk conditions of pregnancy or assess the well-being of the fetus.
There is no ideal method to predict fetal outcome, but a 'non-stress test' through cardiotocography and biophysical profile could provide information about the well-being of the baby at the time of the investigation (Diken 2014).

Role of index test(s)

The role of an index test, if related to an existent test within a diagnostic clinical pathway, can be one of replacement (substitution of the existent test), triage (addition before the existent test), or add-on (addition after the existent test).
TSBA is the existing test for the diagnosis of intrahepatic cholestasis of pregnancy. They are usually assessed after the most common liver tests described above.
CA, glycocholic acid (GCA), CDCA, DCA, LCA, UDCA, UDCA/LCA ratio, total G-c bile acids, total T-c bile acids, total G-c bile acids/total T-c bile acid ratio could be considered as add-on tests after TSBAs. Depending on their diagnostic accuracy, we may consider any of these as a replacement test or tests of the existent ones to improve the current clinical pathway.

Alternative test(s)

Alternative tests which can be used to assess intrahepatic cholestasis of pregnancy through exclusion of possible differential diagnosis may include serum and urinary biochemical tests, or imaging techniques.
In case of suspicion of immunological diseases (e.g. primary biliary cirrhosis, primary sclerosing cholangitis, or other autoimmune diseases), clinicians are advised to test nuclear, smooth muscle, mitochondrial, liver-kidney microsomal autoantibodies, or other organ-specific autoantibodies. In case of suspicion of liver infectious diseases, clinicians are advised to perform blood serology for the most common type of hepatotropic viral agents such as hepatitis A, B, or C viruses; cytomegalovirus; and Epstein-Barr virus.
Among the imaging techniques, if ultrasound does not rule out other cholestatic diseases, then magnetic resonance imaging of the biliary tree or of the abdomen could be used to exclude possible causes of extrahepatic cholestasis such as choledochal stones, tumours of the biliary tree, or tumours of the pancreas (Boregowda 2013).
Liver biopsy is indicated only in jaundiced women without pruritus, beginning of symptoms before week 20 of gestation, and

sustained abnormal laboratory findings beyond eight weeks after delivery (Boregowda 2013). Liver biopsy is not recommended for the diagnosis of intrahepatic cholestasis of pregnancy.

We found some biomarker tests which were studied for their accuracy in diagnosing intrahepatic cholestasis of pregnancy, but they were mostly performed in a research setting. Among them were urinary progesterone metabolites, serum autotaxin activity, and glutathione S-transferase. Urinary progesterone sulphated metabolites were directly related to the pathogenesis of the disease and were studied for the diagnosis of intrahepatic cholestasis of pregnancy and for monitoring response to treatment (Meng 1997; Reyes 2000b; Abu-Hayyeh 2013). Serum autotaxin activity was shown to correlate with cholestasis-associated pruritus and was considered able to distinguish intrahepatic cholestasis of pregnancy from other pruritic disorders of pregnancy or pregnancy-related liver diseases (Kremer 2015). Glutathione S-transferase is a detoxification liver enzyme with ubiquitous distribution in hepatic cells and its blood concentration rapidly increases in cases of acute liver damage (Ozer 2008). Because of this, glutathione S-transferase could be an earlier and more accurate indicator of hepatic dysfunction than liver aminotransferases or total bile acids alone (Dann 2004; Joutsiniemi 2010).

Rationale

Intrahepatic cholestasis of pregnancy is considered a high-risk condition in pregnant women, primarily due to the increased risk of fetal adverse events. Currently, TSBAs are the most used diagnostic and prognostic markers for the disease, while serum bile acid profile components are less commonly used. A diagnostic test accuracy systematic review on TSBAs and serum bile acid profile components has never been published. Thus, assessment of the accuracy of TSBAs and serum bile acid profile components, independently or in combination, and determining which index test (or combination of index tests) are best, may help us to improve the current clinical pathway and clinicians' approaches to the disease, leading to a direct benefit on the outcomes of pregnant women and their babies.

Following this, a prognostic accuracy review to assess the reliability of our index tests also as prognostic markers for the disease could become feasible.

OBJECTIVES

To determine the diagnostic accuracy of total serum bile acids or total serum bile acids profile, or both for the diagnosis of intrahepatic cholestasis of pregnancy in pregnant women presenting with pruritus.

Secondary objectives

To compare the diagnostic accuracy of total serum bile acids and each component of serum bile acid profile, considered independently or in combination, in diagnosing intrahepatic cholestasis of pregnancy; to define the optimal cut-off values for these; and to investigate possible sources of heterogeneity.

METHODS

Criteria for considering studies for this review

Types of studies

We will include prospectively or retrospectively performed diagnostic participant-control (case-control) or cross-sectional studies, irrespective of publication status or language (Colli 2014).

Participants

Pregnant women of any age or ethnicity, recruited in any clinical setting. They should have undergone the reference standard (see Reference standards) and any of the index tests, singly or in combination (see Index tests).

Index tests

We will consider the following index tests, singly or in combination (i.e. TSBAs plus any component of serum bile acid profile):

- total serum bile acids (TSBA);
- cholic acid (CA);
- glycocholic acid (GCA);
- chenodeoxycholic acid (CDCA);
- deoxycholic acid (DCA);
- lithocholic acid (LCA);
- ursodeoxycholic acid (UDCA);
- cholic/chenodeoxycholic acid ratio (CA/CDCA);
- total glyco-conjugated bile acids (G-c);
- total tauro-conjugated bile acids (T-c);
- total glyco-conjugated bile acids/total taurine-conjugated bile acid ratio (G-c/T-c).

Target conditions

Intrahepatic cholestasis of pregnancy defined as pruritus with onset during pregnancy associated with abnormal liver tests, both unexplained by other skin or liver diseases, and which resolves after delivery (Geenes 2009; Green-top Guideline no.43).

Reference standards

Clinical evaluation in which follow-up after delivery is included. In particular, the best reference standard is clinical evaluation considered as the final judgement of the clinician who takes into account the whole clinical assessment of signs and symptoms suggestive for intrahepatic cholestasis of pregnancy; the presence of any otherwise unexplained, persistent abnormalities of aspartate transaminase (AST), alanine aminotransferase (ALT), or bilirubin levels until delivery; and follow-up after delivery assessing spontaneous relief of symptoms and normalisation of liver tests within eight weeks at most. We will judge study definitions of the reference standard to be of lower quality if any of the clinical and laboratory factors are omitted from the definitions.

Search methods for identification of studies

Electronic searches

We will search The Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2017), The Cochrane Hepato-Biliary Group Diagnostic Test of Accuracy Studies Register (Gluud 2017), The Cochrane Pregnancy and Childbirth Group Trials Register, The Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE (OvidSP), Embase (OvidSP), Science Citation Index Expanded (SCI-EXPANDED; Web of Science), CINAHL (EBSCO host), PASCAL, and BIOSIS (Web of Science) (Royle 2003).

We will search Chinese literature with the help of Maoling Wei from the Chinese Cochrane Centre. We will provide details at the review stage.

As the highest prevalence of the disease is observed in Chile, by contacting some South American expert authors, we have been advised to search thoroughly two local databases which are Latino American and the Caribbean (LILACS) and Scientific Electronic Library Online (SCIELO).

We will also search through some field-databases suggested by the Royal College of Obstetricians and Gynaecologists, which are the Evidence Search: Health and Social Care by NICE, POPLINE, The World Health Organization (WHO) Reproductive Health Library (RHL), and The Turning Research into Practice database (TRIP).

We will apply no language or document-type restrictions.

We have given the preliminary search strategies with the expected time spans of the searches in Appendix 1.

Searching other resources

We will identify additional references by handsearching the references of articles, meta-analyses, and evidence-based guidelines retrieved from the computerised databases, and the references suggested by the 'ICP support' website (www.icpsupport.org/papers.shtml), to identify other potentially relevant studies for inclusion in our review.

We will search for dissertations and theses through ProQuest Dissertations & Thesis Database and Index to Theses in Great Britain and Ireland, and grey literature through OpenSIGLE and National Technical Information Service (NTIS).

We will search online trial registries such as ClinicalTrial.gov (clinicaltrials.gov/), European Medicines Agency (EMA) (www.ema.europa.eu/ema/), WHO International Clinical Trial Registry Platform (www.who.int/ictrp), the Food and Drug Administration (FDA) (www.fda.gov), and pharmaceutical company sources as well as contacting experts in the field for ongoing or unpublished trials.

Data collection and analysis

We will follow the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy* (Macaskill 2010).

Selection of studies

Two review authors (CM, TS) will independently conduct the first selection of studies by reading titles or abstracts, or both, of the identified studies. The two review authors will independently review the full texts for eligibility, assessing the fulfilment of the inclusion criteria. During this second selection stage, if the two review authors find multiple publications of one study fulfilling the inclusion criteria, they will group them together and they will screen these publications for complimentary data or check them for discrepancies. If in doubt, the review authors will write e-mails to study authors to ensure that publications refer to the same study and to check the correctness of data. During this process, the two authors will classify study references as either Included studies or Excluded studies, completing also the Characteristics of included studies and Characteristics of excluded studies.

We will solve disagreements by discussion or by consulting a third review author (CG, GC, or DN).

Data extraction and management

Two review authors (CN, TS) will independently extract data from each included study. They will solve disagreements by discussion or by consulting a third review author (CG, GC, or DN).

They will retrieve the following study data:

- general information: title, journal, year, publication status, study design (cross-sectional or participant-control, prospective or retrospective, single centre or multicentre), time span;
- total number of women screened for inclusion, number of pregnant women included, and prevalence of the disease in the considered population;
- baseline characteristics: age, ethnicity, country, if pregnancies were multiple or single, week of pregnancy in which

the index tests were performed, disease severity, and concurrent medications used;

- if most common liver tests were performed, and their findings;
- index tests (TSBAs or any component of serum bile acid profile): technique used for the measurement, fasting or postprandial status of women when the test was performed, and predefined cut-off values for the diagnosis;
- follow-up after delivery: length of follow-up, length of time needed for assessment of the spontaneous relief of symptoms, and normalisation of liver tests;
- number of true positive (TP), true negative (TN), false positive (FP), and false negative (FN) results comparing index test results with reference standard;
- information related to the QUADAS-2 items for evaluation of the risk of bias of the studies (Whiting 2011).

The two review authors will summarise data from each study in two by two tables (FP, FN, TP, TN) and will enter the data into Review Manager 5 (RevMan 2014).

Missing data

If information on any of the FP, FN, TP, or TN diagnostic test values are missing, we will attempt to contact the authors of the included studies to obtain missing information. We will also contact authors if other types of information needed for this review are missing, especially when the publication is an abstract or poster presentation. We will use Excel and Review Manager 5 to add data required for statistical analyses (RevMan 2014).

We will contact primary authors for missing data by e-mail. In the absence of a reply, we will send a second e-mail one week later, or we will contact the study authors by telephone. We will acknowledge study authors for providing missing data, and we will create references to unpublished studies following the Cochrane Style Manual (community.cochrane.org/book˙pdf/224) when such study data are obtained through personal communication.

We will exclude the studies if we cannot obtain the data needed for the two by two tables.

Assessment of methodological quality

Design flaws in test accuracy studies can produce biased results (Lijmer 1999; Whiting 2004; Rutjes 2006). In addition, evaluation of study results is quite often impossible due to incomplete reporting (Smidt 2005).

To limit the influence of different biases, two review authors will independently assess the risk of bias of the included studies using QUADAS-2 domains (Whiting 2011). A third review author will check the extraction of data concerning the assessment of the risk of bias. We will resolve disagreements by discussion or by consulting a fourth review author. We will contact study authors if information on methodology is lacking in order to assess correctly the risk of bias of the studies.

We will adopt the domains in Appendix 2 to address aspects of study quality involving the participant spectrum, index test, reference standard, and flow and timing. We will classify a study at low risk of bias only if classified at 'low risk of bias' in all the four domains (participant spectrum, index test, reference standard, and flow and timing); otherwise, we will consider the study at high risk of bias (Jüni 1999; Whiting 2005).

We will use tabular and graphical displays to summarise QUADAS-2 assessments.

Statistical analysis and data synthesis

We will carry out the analyses following Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy* (Macaskill 2010). We will use the Review Manager 5 software for analyses and forest plots (RevMan 2014).

We will build two by two tables for each primary study and for all the index tests considered. We will estimate sensitivity, specificity, and positive and negative likelihood ratios (LR+ and LR-) with their 95% confidence intervals (CI). We plan to present data in coupled forest plots, showing sensitivities and specificities of each study, with their 95% CI. We plan to plot the studies in the receiver operator characteristic (ROC) space, reporting sensitivity against 1 - specificity.

If included studies show very heterogeneous results or are at high risk of bias, we might not perform meta-analyses, or, if we decide to conduct such meta-analyses, then we will be cautious with interpretation of the results.

If the included primary studies report accuracy data using different cut-off values, we will adopt the hierarchical summary ROC model (HSROC) to pool data and to estimate a summary ROC (SROC) curve. If a sufficient number of primary studies report data using common cut-off values, we will perform meta-analyses using the bivariate model and we will provide the estimate of the summary operating point (the point with mean sensitivity and mean specificity) at those cut-off values.

For primary studies which reported accuracy results for more than one cut-off point, we will report sensitivities and specificities for all the cut-off points. We will include only one cut-off point (the most commonly reported) when we perform the HSROC analysis. On the contrary, we will include all the relevant cut-off points when we perform the bivariate analysis considering the studies which share a common cut-off value.

We will make direct and indirect comparisons of the considered index tests by adding the index tests as covariates to the bivariate or HSROC model.

We will use SAS statistical software, release 9.4 (SAS Institute Inc., Cary, NC, USA) to perform all statistical analyses.

Investigations of heterogeneity

We will investigate heterogeneity first by visual inspection of the paired forest plots of sensitivities and specificities for each index test. Subsequently, we will perform a formal analysis, where appropriate, by adding covariates to the bivariate or HSROC model. We will consider the following as possible sources of heterogeneity:

- country in which the study took place;
- participant selection: studies including only pregnant women with suspicion of intrahepatic cholestasis of pregnancy versus studies including all pregnant women;
- laboratory techniques used for the measurement of the index tests;
- participant treatment with UDCA versus no treatment;
- fasting or postprandial status of pregnant women at the time when the serum samples were taken;
- timing of assessment of the index test(s): the time when the symptoms arose, the peak values among multiple assessments during pregnancy, immediately before delivery;
- differences in study definitions of intrahepatic cholestasis of pregnancy.

Sensitivity analyses

We will perform sensitivity analyses by excluding studies at high risk of bias (studies judged as high risk of bias or unclear risk of bias in at least one of the domains of QUADAS-2) to explore the influence of the quality of the included studies.
Then, we will perform different sensitivity analyses as follows:

- excluding all studies with participant-control (case-control) design;
- excluding only studies with participant-control design which enrolled as controls asymptomatic pregnant women (i.e. without symptoms suggestive for cholestasis);
- excluding studies in which the index test was part of the reference standard.

If the planned sensitivity analyses show robustness of the main analysis, we will use the results of the main analysis for drawing conclusions. Otherwise, in case of discrepancies between the results of the main and the sensitivity analyses, we will use the results of the sensitivity analysis (only studies at low risk of bias) for drawing conclusions.

Assessment of reporting bias

We will produce a funnel plot to investigate reporting bias visually, using the statistical method suggested by Deeks and colleagues (Deeks 2005).

'Summary of findings' table

To construct a 'Summary of findings' table for presenting the key findings of our review, we will use the approach developed by The Cochrane GRADEing group (formerly, The Cochrane Applicability and Recommendations Methods Group) which is in conformity with the QUADAS-2 (see Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy*, Whiting 2011; Bossuyt 2013). Thus, in our 'Summary of findings' table, we will include key information on the review question and its components (population, setting, index tests, role and purpose of tests, and reference standard), providing accuracy estimates, the available data (number of participants and studies), quality of the included studies, and the practical implications of the results (by providing prevalence estimates and calculating women with FP and FN results in a cohort of 1000 women with suspected intrahepatic cholestasis of pregnancy). The quality of evidence in a 'Summary of findings' table refers to the degree to which study methods avoided risk of bias in estimates of diagnostic accuracy and the extent to which primary studies are applicable to the research question (The Cochrane GRADEing group). To make a judgement on how reliable summary estimates are, we will indicate if studies are at high risk of bias: where studies are at high risk of bias, we will recommend cautious application of the results of our review in clinical practice.

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Peer reviewers: Theis Lange, Denmark; William Huang, US; Emanuela Wally Ossola, Italy; Yannick Bacq, France.

Peer reviewers from the Cochrane UK Diagnostic Test Accuracy Review Editorial Team - anonymous.

Contact editor: Agostino Colli, Italy.

Sign-off editor: Agostino Colli, Italy.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Preliminary search strategies

Database	Time span	Preliminary search strategies
The Cochrane Hepato-Biliary Group Controlled Trials Register	Date will be given at review stage.	(((bile or cholic or glycocholic or chenodeox*cholic or deox*cholic or lithocholic or ursodeox*cholic or glyco-conjugated or tauro-conjugated or glycine or taurine) and acid*) or (chol*glycine or TSBA or CA or GCA or CDCA or LCA or DCA or UDCA)) AND ((cholesta* and (hepat* or liver*)) or jaundice or (icterus gravidarum)) AND (pregnan* or obstetric* or gestation*)
The Cochrane Pregnancy and Childbirth Group Trials Register	Date will be given at review stage.	(((bile or cholic or glycocholic or chenodeox*cholic or deox*cholic or lithocholic or ursodeox*cholic or glyco-conjugated or tauro-conjugated or glycine or

(*Continued*)

		taurine) and acid*) or (chol*glycine or TSBA or CA or GCA or CDCA or LCA or DCA or UDCA)) AND ((cholesta* and (hepat* or liver*)) or jaundice or (icterus gravidarum)) AND (pregnan* or obstetric* or gestation*)
The Cochrane Hepato-Biliary Group Diagnostic Test of Accuracy Studies Register	Date will be given at review stage.	(((bile or cholic or glycocholic or chenodeox*cholic or deox*cholic or lithocholic or ursodeox*cholic or glyco-conjugated or tauro-conjugated or glycine or taurine) and acid*) or (chol*glycine or TSBA or CA or GCA or CDCA or LCA or DCA or UDCA)) AND ((cholesta* and (hepat* or liver*)) or (jaundice or (icterus gravidarum)) AND (pregnan* or obstetric* or gestation*)
The Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library	Latest issue	#1 MeSH descriptor: [Bile Acids and Salts] explode all trees #2 ((bile or cholic or glycocholic or chenodeox*cholic or deox*cholic or lithocholic or ursodeox*cholic or glyco-conjugated or tauro-conjugated or glycine or taurine) and acid*) or (chol*glycine or TSBA or CA or GCA or CDCA or LCA or DCA or UDCA) #3 #1 or #2 #4 MeSH descriptor: [Cholestasis, Intrahepatic] explode all trees #5 (cholesta* and (hepat* or liver*)) or jaundice or (icterus gravidarum) #6 #4 or #5 #7 MeSH descriptor: [Pregnancy] explode all trees #8 pregnan* or obstetric* or gestation* #9 #7 or #8 #10 #3 and #6 and #9
MEDLINE (OvidSP)	1946 to the date of search	1. exp "Bile Acids and Salts"/ 2. ((bile or cholic or glycocholic or chenodeox*cholic or deox*cholic or lithocholic or ursodeox*cholic or glyco-conjugated or tauro-conjugated or glycine or taurine) and acid* or (chol*glycine or TSBA or CA or GCA or CDCA or LCA or DCA or UDCA)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. 1 or 2 4. exp Cholestasis, Intrahepatic/ 5. ((cholesta* and (hepat* or liver*)) or jaundice or icterus gravidarum).mp. [mp=title, abstract, orig-

(*Continued*)

		inal title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 6. 4 or 5 7. exp Pregnancy/ 8. (pregnan* or obstetric* or gestation*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 9. 7 or 8 10. 3 and 6 and 9
Embase (OvidSP)	1974 to the date of search	1. exp bile acid/ 2. (((bile or cholic or glycocholic or chenodeox*cholic or deox*cholic or lithocholic or ursodeox*cholic or glyco-conjugated or tauro-conjugated or glycine or taurine) and acid*) or (chol*glycine or TSBA or CA or GCA or CDCA or LCA or DCA or UDCA)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 3. 1 or 2 4. exp intrahepatic cholestasis/ 5. ((cholesta* and (hepat* or liver*)) or jaundice or (icterus gravidarum)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 6. 4 or 5 7. exp pregnancy/ 8. (pregnan* or obstetric* or gestation*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 9. 7 or 8 10. 3 and 6 and 9
Science Citation Index Expanded (Web of Science)	1900 to the date of search	#4 #1 AND #2 AND #3 #3 TS=(pregnan* or obstetric* or gestation*) #2 TS=((cholesta* and (hepat* or liver*)) or jaundice or (icterus gravidarum)) #1 TS=((bile or cholic or glycocholic or chenodeox*cholic or deox*cholic or lithocholic or ursodeox*cholic or glyco-conjugated or tauro-conjugated or glycine or taurine) and acid*) or

(*Continued*)

		(chol*glycine or CA or GCA or CDCA or LCA or DCA or UDCA))
CINAHL (EBSCO host)	1981 to the date of search.	S10 S6 AND S9 S9 S8 OR S7 S8 TX pregnan* or obstetric* or gestation* S7 MW Pregnancy S6 S4 OR S5 S5 TX (cholesta* and (hepat* or liver*)) or jaundice or (icterus gravidarum) S4 MW Intrahepatic Cholestasis S3 S1 OR S2 S2 TX ((bile or cholic or glycocholic or chenodeox? cholic or deox?cholic or lithocholic or ursodeox? cholic or glyco-conjugated or tauro-conjugated or glycine or taurine) and acid?) or (chol?glycine or TSBA or CA or GCA or CDCA or LCA or DCA or UDCA) S1 MW Bile Acids and Salts
BIOSIS Previews (Web of Science)	1969 to the date of search	#4 #1 AND #2 AND #3 #3 TS=(pregnan* or obstetric* or gestation*) #2 TS=((cholesta* and (hepat* or liver*)) or jaundice or (icterus gravidarum)) #1 TS=(((bile or cholic or glycocholic or chenodeox*cholic or deox*cholic or lithocholic or ursodeox*cholic or glyco-conjugated or tauro-conjugated or glycine or taurine) and acid*) or (chol*glycine or TSBA or CA or GCA or CDCA or LCA or DCA or UDCA))
LILACS (VHL)	Date will be given at review stage.	1. (tw:((tw:(cholestasis)) AND (tw:(pregnancy OR obstetric)))) OR (tw:((tw:(colestasis)) AND (tw:(gravídica OR (intrahepática AND embarazo) OR obstétrica)))) OR (tw:((tw:(ictericia)) AND (tw:(embarazo OR gravídica)))) OR (tw:((tw:(colestase)) AND (tw:(gravidez OR gestacional OR obstétrica)))) OR (tw:((tw:(icterícia)) AND (tw:(gravidez OR colestática)))) AND (instance:"regional") AND (db:("LILACS")) 2. (tw:(acidos biliares)) AND (tw:(embarazo OR gravidez OR obstétrica OR gestational OR gravidica)) AND (instance:"regional") AND (db:("LILACS")) 3. (((mh:("Bile Acids and Salts")) OR (tw:(acidos biliares))) AND ((mh:("Cholestasis, Intrahepatic")) OR (tw:(cholestasis OR colestasis OR colestase OR ictericia))) AND ((mh:("Pregnancy Complications")) OR (tw:(pregnancy OR obstet-

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		ric OR gravídica OR embarazo OR obstétrica OR gravidez OR gestacional)))) AND (instance:"regional") AND (db:("LILACS"))
SCIELO	Date will be given at review stage.	1. ((cholestasis) AND (pregnancy OR obstetric)) OR ((colestasis) AND (embarazo OR obstétrica)) OR ((ictericia) AND (embarazo OR gravídica)) OR ((icterícia) AND (gravidez OR colestática)) OR ((colestase) AND (gravidez OR gestacional)) 2. (bile acids) AND (pregnancy OR obstetric) 3. (acidos biliares) AND (embarazo OR gravidez OR obstétrica OR gestational OR gravidica) 4. ((cholestasis) AND (pregnancy OR obstetric)) OR ((colestasis) AND (embarazo OR obstétrica)) OR ((ictericia) AND (embarazo OR gravídica)) OR ((icterícia) AND (gravidez OR colestática)) OR ((colestase) AND (gravidez OR gestacional)) OR ((bile acids) AND (pregnancy OR obstetric)) OR ((acidos biliares) AND (embarazo OR gravidez OR obstétrica OR gestational OR gravidica))
TRIP, RHL, Evidence search: Health and Social Care, OpenSIGLE, NTIS	Date will be given at review stage.	1. cholestasis AND (obstetric OR pregnancy OR pregnant OR gestation OR gestational) 2. (obstetric OR pregnancy OR pregnant OR gestation OR gestational) AND ((bile acid) OR (bile acids) OR (bile salt) OR (bile salts)) 3. cholestasis AND (obstetric OR pregnancy OR pregnant OR gestation OR gestational) AND ((bile acid) OR (bile acids) OR (bile salt) OR (bile salts)) 4. (icterus OR jaundice OR pruritus) AND (gravidarum OR pregnancy OR obstetric) 5. (cholestasis OR (bile acid) OR (bile acids) OR (bile salt) OR (bile salts)) AND (obstetric OR pregnancy OR pregnant OR gestation OR gestational) OR ((icterus OR jaundice OR pruritus) AND (gravidarum OR pregnancy OR obstetric))
Chinese databases (CNKI, VIP)	Date will be given at review stage.	Search strategies in Chinese can be obtained by contacting the first review author, CM

Appendix 2. QUADAS-2

Domain	Participant selection	Index test	Reference standard	Flow and timing
Description	**Describe methods of participant selection: describe inclusion criteria for participants (prior testing, presentation, intended use of index test, and setting):** The studies that fulfil the inclusion criteria of this review should have included pregnant women recruited in any clinical setting They should have been evaluated for personal history of skin or liver diseases, presence of pruritus during their pregnancy, and been assessed with any of the most common liver test (or tests), followed by any of the already mentioned index tests (total bile acids, cholic acid, glycocholic acid, chenodeoxycholic acid, deoxycholic acid, lithocholic acid, ursodeoxycholic acid, cholic/chenodeoxycholic acids, total glyco-conjugated bile acids, total tauro-conjugated bile acids, total glyco-conjugated bile acids/total taurine-conjugated bile acids)	**Describe the index test and how it was conducted and interpreted:** The index tests (total bile acids, cholic acid, glycocholic acid, chenodeoxycholic acid, deoxycholic acid, lithocholic acid, ursodeoxycholic acid, cholic/chenodeoxycholic acids, total glyco-conjugated bile acids, total tauro-conjugated bile acids, total glyco-conjugated bile acids/total taurine-conjugated bile acids) are non-invasive laboratory serum tests performed after the first clinical evaluation of the pregnant women for the diagnosis of intrahepatic cholestasis of pregnancy. The serum concentration of the index test(s) can be assessed through different techniques. Laboratory methods and diagnostic cut-off values could vary between studies	**Describe the reference standard and how it was conducted and interpreted:** Clinical evaluation including follow-up after delivery. The clinical evaluation is the final judgement of the clinician who takes into account the clinical assessment of suggestive signs and symptoms for intrahepatic cholestasis of pregnancy and the presence of any otherwise unexplained, persistent abnormalities of aspartate transaminase, alanine aminotransferase, or bilirubin levels until delivery. The follow-up after delivery is the assessment of spontaneous relief of symptoms and normalisation of liver tests within 8 weeks at most	**Describe any people who did not receive the index test(s) or reference standard (or both) or who will be excluded from the 2 ×2 table (refer to flow diagram): describe the time interval and any interventions between index test(s) and reference standard:** Pregnant women considered for inclusion should have undergone the reference standard and any of the index tests, singly or in combination (see Reference standards, Index tests and clinical diagnostic pathway represented in Figure 2). We will exclude participants who lack data for the 2 × 2 table To define a time interval between our index tests and our reference standard is not relevant, as the index tests should be performed when the suspicion of intrahepatic cholestasis of pregnancy arises and the reference standard comprises the follow-up after delivery
Signalling questions: yes/no/unclear	**Was a consecutive or random sample of participants enrolled?** Yes: all consecutive participants or random sample of people with suspected in-	**Were the index test results interpreted without knowledge of the results of the reference standard?** Yes: the index test results were interpreted without	**Is the reference standard likely to classify the target condition correctly?** Yes: if participants underwent a thorough clinical evaluation excluding	**Was there an appropriate interval between index test(s) and reference standard?** This is not a relevant question to our review.

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	trahepatic cholestasis of pregnancy were enrolled in the study No: selected participants were not included. Unclear: insufficient data were reported to permit a judgement	knowledge of the results of the reference standard No: the index test results were not interpreted without knowledge of the results of the reference standard Unclear: insufficient data were reported to permit a judgement	all possible differential diagnoses and if they underwent an adequate follow-up after delivery assessing the spontaneous relief of symptoms and normalisation of the previously found abnormal liver tests No: clinical evaluation including the follow-up after delivery was not able to rule out other possible differential diagnosis Unclear: insufficient data were reported to permit a judgement	
	Was a participant-control design avoided? Yes: participant-control design was avoided. No: participant-control design was not avoided. Unclear: insufficient information was reported to permit a judgement	**If a threshold was used, was it prespecified?** Yes: the threshold was prespecified. No: the threshold was not prespecified. Unclear: it was not reported or not clearly described.	**Were the reference standard results interpreted without knowledge of the results of the index test?** Yes: clinical evaluation including the follow-up after delivery was performed without knowledge of the results of TSBAs or any component of serum bile acid profile No: clinical evaluation including the follow-up after delivery was performed with knowledge of the results of TSBAs or any component of serum bile acid profile Unclear: insufficient data were reported to permit a judgement	**Did all participants receive the reference standard?** Yes: all participants underwent the reference standard, i.e. clinical evaluation including the follow-up after delivery No: not all participants underwent the reference standard, i.e. clinical evaluation including the follow-up after delivery Unclear: insufficient data were reported to permit a judgement
	Did the study avoid inappropriate exclusions? Yes: the study avoided inappropriate exclusions (e.g. women having a previously assessed value		**Was the index test evaluation not part of the reference standard?** Yes: the index test evaluation was not part of the reference standard	**Did all participants receive the same reference standard?** Yes: all participants received the same reference standard (i.e. clini-

(*Continued*)

	of the index test(s) below a defined cut-off) No: the study excluded participants inappropriately. Unclear: insufficient data were reported to permit a judgement		No: index test evaluation was part of the reference standard Unclear: insufficient data were reported to permit a judgement	cal evaluation including the follow-up after delivery) No: not all participants received the same reference standard (i.e. clinical evaluation including the follow-up after delivery) Unclear: insufficient data were reported to permit a judgement **Were all participants included in the analysis?** Yes: all participants meeting the selection criteria were included in the analysis, or data on all the selected participants were available so that a 2 × 2 table including all selected participants could be constructed No: not all participants meeting the selection criteria were included in the analysis or the 2 × 2 table could not be constructed using data on all selected participants Unclear: insufficient data were reported to permit a judgement
Risk of bias: high/low/unclear	**Could the selection of participants have introduced bias?** High risk of bias: yes, if the selection of participants introduced bias Low risk of bias: no, if the selection of participants had not introduced bias Unclear risk of bias: insufficient data were re-	**Could the conduct or interpretation of the index test have introduced bias?** High risk of bias: if the answer to the signalling questions on the conduct or interpretation of the index test was 'no' Low risk of bias: if the answer to the signalling questions on the conduct	**Could the reference standard, its conduct, or its interpretation have introduced bias?** High risk of bias: if the answer to the signalling questions on the reference standard, its conduct, or its interpretation was 'no' Low risk of bias: if the	**Could the participant flow have introduced bias?** High risk of bias: if the answer to the signalling questions on flow and timing was 'no' Low risk of bias: if the answer to the signalling questions on flow and timing was 'yes' Unclear risk of bias: if

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	ported to permit a judgement on the risk of bias	or interpretation of the index test was 'yes' Unclear risk of bias: if the answers to the 2 signalling questions on the conduct or interpretation of the index test were either 'unclear' or any combination of 'unclear' with 'yes' or 'no'	answer to the signalling questions on the reference standard, its conduct, or its interpretation was 'yes' Unclear risk of bias: if the answers to the 3 signalling questions on the reference standard, its conduct, or its interpretation were either 'unclear' or any combination of 'unclear' with 'yes' or 'no'	the answers to the 4 signalling questions on flow and timing were either 'unclear' or any combination of 'unclear' with 'yes' or 'no'
Concerns regarding applicability: high/low/unclear	**Are there concerns that the included participants do not match the review question?** High concern: there was high concern that the included participants did not match the review question Low concern: there was low concern that the included participants did not match the review question Unclear concern: if it was unclear.	**Are there concerns that the index test, its conduct, or interpretation differ from the review question?** High concern: there was high concern that the conduct or interpretation of TSBAs or any component of serum bile acid profile differed from the way likely to be used in clinical practice Low concern: there was low concern that the conduct or interpretation of TSBAs or any component of serum bile acid profile differed from the way likely to be used in clinical practice Unclear concern: if it was unclear.	**Are there concerns that the target condition as defined by the reference standard does not match the review question?** High concern: all participants did not undergo clinical evaluation including the follow-up after delivery Low concern: all participants underwent clinical evaluation including the follow-up after delivery Unclear concern: if it was unclear.	-

TSBA: total serum bile acid.

CONTRIBUTIONS OF AUTHORS

CM: formulated the research question and drafted the protocol.

GC: provided statistical expert opinion, involved in decision making, and revised the protocol.

TS: provided content expert opinion and revised the protocol.

DN: provided advice, involved in decision making, and commented upon and revised the protocol.

CG: provided methodological expert opinion, involved in decision making, and revised the protocol.

All authors approved the protocol.

DECLARATIONS OF INTEREST

None known.

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