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

Manzotti, Cristina; Casazza, Giovanni; Štimac, Tea; Nikolova, Dimitrinka; Gluud, Christian

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[Diagnostic Test Accuracy Review]

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

Cristina Manzotti[1,2,3], Giovanni Casazza[4], Tea Stimac[5], Dimitrinka Nikolova[6], Christian Gluud[6]

[1]Obstetrics and Gynecology Department, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy. [2]Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [3]Gastro-Intestinal Unit, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy. [4]Dipartimento di Scienze Biomediche e Cliniche "L. Sacco", Università degli Studi di Milano, Milan, Italy. [5]Obstetrics and Gynecology, Clinical Hospital Centre Rijeka, Rijeka, Croatia. [6]Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Contact address: Cristina Manzotti, Obstetrics and Gynecology Department, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Università degli Studi di Milano, Via Commenda 12 - Clinica Mangiagalli, piano terra, Milan, Milan, 20122, Italy. cristina.manzotti1@gmail.com, cristina.manzotti@unimi.it.

ABSTRACT

Background

Intrahepatic cholestasis of pregnancy is a pregnancy-specific liver disorder, possibly associated with an increased risk of severe fetal adverse events. Total serum bile acids (TSBA) concentration, alone or in combination with serum aminotransferases, have been the most often used biomarkers for the diagnosis of intrahepatic cholestasis of pregnancy in clinical practice. Serum bile acid profile, composed of primary or secondary, conjugated or non-conjugated bile acids, may provide more specific disease information.

Objectives

To assess and compare, independently or in combination, the diagnostic accuracy of total serum bile acids or serum bile acids profile, or both, for the diagnosis of intrahepatic cholestasis of pregnancy in pregnant women, presenting with pruritus. To define the optimal cut-off values for components of serum bile acid profile; to investigate possible sources of heterogeneity.

Search methods

We searched the Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Hepato-Biliary Group Diagnostic Test Accuracy Studies Register, the Cochrane Library, MEDLINE Ovid, Embase Ovid, Science Citation Index Expanded, Conference Proceedings Citation Index – Science, BIOSIS, CINAHL, two Chinese databases (CKNI, VIP), Latin American and Caribbean Health Sciences Literature (LILACS), Scientific Electronic Library Online (SciELO), Evidence Search: Health and Social Care by the National Institute for Health and Care Excellence (NICE), the World Health Organization (WHO) Reproductive Health Library (RHL), and the Turning Research into Practice database (TRIP). The most recent date of search was 6 May 2019. We identified additional references by handsearching the references of articles, meta-analyses, and evidence-based guidelines retrieved from the computerised databases, on-line trial registries, and grey literature through OpenSIGLE, National Technical Information Service (NTIS), ProQuest Dissertations & Thesis Database, and Index to Theses in Great Britain and Ireland.

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Selection criteria

Prospective or retrospective diagnostic case-control or cross-sectional studies, irrespective of publication date, format, and language, which evaluated the diagnostic accuracy of total serum bile acids (TSBA) or components of serum bile acid profile for the diagnosis of intrahepatic cholestasis of pregnancy in pregnant women of any age or ethnicity, in any clinical setting, symptomatic for pruritus.

Data collection and analysis

We selected studies by reading titles, abstracts, or full texts, and assessing their fulfilment of our inclusion criteria. We emailed primary authors to request missing data or individual participant data. Having extracted data from each included study, we built the two-by-two tables for each primary study and for all the index tests considered. We estimated sensitivity and specificity with their 95% confidence intervals (CI). We presented data in coupled forest plots, showing sensitivities and specificities of each study, and we plotted the studies in the Receiver Operating Characteristic (ROC) space. We performed meta-analyses adopting the hierarchical summary ROC model (HSROC) or the bivariate model to meta-analyse the data. We made indirect comparisons of the considered index tests by adding the index tests as covariates to the bivariate or HSROC models. We performed heterogeneity analysis and sensitivity analysis on studies assessing TSBA accuracy. We used Review Manager 5 (RevMan 5) and SAS statistical software, release 9.4 (SAS Institute Inc., Cary, NC, USA), to perform all statistical analyses. We used QUADAS-2 domains to assess the risk of bias of the included studies.

Main results

Our search yielded 5073 references, but at the end of our selection process, only 16 studies fulfilled the review inclusion criteria. Nine of these provided individual participant data. We analysed only data concerning TSBA, cholic acid (CA), glycocholic acid (GCA), chenodeoxycholic acid (CDCA), and CA/CDCA because the remaining planned index tests were assessed in few studies. Only one study had low risk of bias in all four QUADAS-2 domains. The most biased domains were the patient sampling and the reference standard domains. When considering all studies with a cut-off of 10 µmol/L, TSBA overall sensitivity ranged from 0.72 to 0.98 and specificity ranged from 0.81 to 0.97. After a sensitivity analysis excluding case-control studies, TSBA sensitivity ranged from 0.48 to 0.66 and specificity from 0.52 to 0.99. After a sensitivity analysis excluding studies in which TSBA was part of the reference standard, TSBA sensitivity ranged from 0.49 to 0.65 and specificity from 0.53 to 0.99. We found the estimates of the overall accuracy for some serum bile acid components (CA, GCA, CDCA, and CA/CDCA) to be imprecise, with the CI for sensitivity and specificity very wide or impossible to calculate. Indirect comparisons between serum bile acid profile components and TSBA were not statistically significant. None of the heterogeneity analysis performed was statistically significant, except for the timing of assessment of TSBA (onset of symptoms, peak value among multiple assessments, delivery) but without clinically relevant results. We could not analyse the diagnostic accuracy of combinations of index tests because none of the included studies carried them out, and because of the small number of included studies.

Authors' conclusions

The overall high risk of bias, the existing concern regarding applicability of the results in clinical practice, and the great heterogeneity of the results in the included studies prevents us from making recommendations and reaching definitive conclusions at the present time. Thus, we do not find any compelling evidence to recommend or refute the routine use of any of these tests in clinical practice. So far, the diagnostic accuracy of TSBA for intrahepatic cholestasis of pregnancy might have been overestimated. There were too few studies to permit a precise estimate of the accuracy of serum bile acid profile components. Further primary clinical research is mandatory. We need both further phase II and phase III diagnostic studies.

P L A I N   L A N G U A G E   S U M M A R Y

Diagnostic accuracy of total serum bile acids or individual bile acids for intrahepatic cholestasis of pregnancy in woman claiming pruritus

Review question

To assess and compare the diagnostic accuracy of total serum bile acids (TSBA) and some components of serum bile acid profile for the diagnosis of intrahepatic cholestasis of pregnancy in woman with onset of pruritus during pregnancy.

Background

'Diagnostic accuracy' means how well a test correctly identifies or rules out disease and informs subsequent decisions about treatment. Intrahepatic cholestasis of pregnancy is a pregnancy-specific liver disorder, in which bile (a digestive fluid) builds up in the liver, impairing the liver (intrahepatic) function. Intrahepatic cholestasis of pregnancy is possibly associated with an increased risk of premature delivery and fetal death, which seems to occur most often during the last weeks of pregnancy. This is why most clinicians choose to induce early delivery of the baby.

In clinical practice, presence of severe pruritus (itchiness) during late pregnancy and 'otherwise unexplained' abnormalities in serum liver tests, seems enough to support the diagnosis of intrahepatic cholestasis of pregnancy. However, excluding all other possible underlying diseases is not always easy; hence confirmation of the intrahepatic cholestasis of pregnancy diagnosis may be possible only after delivery, when spontaneous disappearance of pruritus and improvement of liver tests on blood exams usually occur.

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Total serum bile acids (TSBA) are the most used biomarkers for intrahepatic cholestasis of pregnancy in clinical practice. Some components of the serum bile acid profile might provide more specific information than total serum bile acids when diagnosing the disease, defining its severity and monitoring its response to treatment.

Study characteristics

This review considered all evidence provided by studies that assess the diagnostic accuracy of total serum bile acids (TSBA) and any component of serum bile acid profile for intrahepatic cholestasis of pregnancy in woman claiming onset of pruritus during pregnancy.

We assessed all available reports from a wide, systematic search of databases of medical literature, irrespective of design, publication status, language, and study design. We finally included 16 studies, most of them assessing the accuracy (sensitivity and specificity) of TSBA with a cut-off of 10 μmol/L. Most studies had a case-control design, and these studies could have overestimated the diagnostic accuracy.

Key results

When considering the studies with a cut-off of 10 μmol/L for TSBA serum concentration, TSBA overall sensitivity (the ability to correctly identify women with the disease) ranged from 72% to 98% and specificity (the ability to correctly identify women without the disease) ranged from 81% to 97%. However, after performing two different analyses excluding studies with probably less reliable results, the diagnostic accuracy seemed lower. We calculated the overall accuracy also of some components of serum bile acid profile, but the small number of studies and the high variability of the results led to very imprecise data.

Quality of the evidence

Only one of the 16 included studies was performed and reported well (low risk of bias). The remaining 15 studies had problems with study design or reporting (high risk of bias). Only five studies seemed to show low concern regarding applicability of the results in clinical practice.

Conclusions

The overall high risk of bias, the existing concern regarding applicability of the results in clinical practice, and the poor uniformity of our results in the included studies prevents us from making recommendations and reaching definitive conclusions at present. Thus, we do not find any compelling evidence to recommend or refute the routine use of any of these tests in clinical practice. So far, the diagnostic accuracy of TSBA for intrahepatic cholestasis of pregnancy might have been overestimated. There were too few studies to permit a precise estimate of the accuracy of serum bile acid profile components. Further primary clinical research is mandatory. We need both further phase II and phase III diagnostic studies.

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SUMMARY OF FINDINGS

Summary of findings 1.   Summary of findings table

What is the diagnostic accuracy of total serum bile acids (TSBA), cholic acid (CA), glycocholic acid (GCA), chenodeoxycholic acid (CDCA), or CA/CDCA for intrahepatic cholestasis of pregnancy (ICP), at different cut-off values?	
Patients/population	Pregnant women with onset of pruritus from the second trimester or later
Prior testing	History, serum tests, liver ultrasound
Settings	Obstetrics and Gynaecology departments
Index test	TSBA, CA, GCA, CDCA, CA/CDCA
Importance	Early diagnosis, treatment and follow-up to reduce fetal adverse events
Reference standard	Clinical evaluation comprising common liver function tests, with exclusion of other possible underlying liver or dermatological diseases, and follow-up after delivery assessing spontaneous normalization of signs and symptoms.
Studies	Cross-sectional and case-control studies. Each study can be present in more than one subgroup and for more than one index test

Test/Sub-group	Summary accuracy (95% CI)	N° part. (studies)	Median prevalence of ICP in pregnant women with pruritus	Implications for an hypothetical population of 100 pregnant women with pruritus	Quality and Comments
TSBA, any cut-off	Sensitivity 0.88 (0.73 to 0.95) Specificity 0.90 (0.84 to 0.95)	1645 (13)	30% (300 out of 1000 pregnant women with pruritus having ICP)	36 (15 to 81) women with ICP would be missed, and 70 (35 to 112) without ICP would be falsely diagnosed.	The overall accuracy found may be not applicable to a real clinical context, as most studies were at high risk of bias for patient selection and reference standard.
TSBA cut-off = 10 μmol/L	Sensitivity 0.91 (0.72 to 0.98) Specificity 0.93 (0.81 to 0.97)	839 (11)	30% (300 out of 1000 pregnant women with pruritus having ICP)	27 (6 to 84) women with ICP would be missed, and 49 (21 to 133) without ICP would be falsely diagnosed.	The overall accuracy found may be not applicable to a real clinical context, as most studies were at high risk of bias for patient selection and reference standard.

CA cut-off = 2 μmol/L	Sensitivity 0.99 (0.33 to 1.00) Specificity 0.61 (0.23to 0.89)	312 (4)	---	---	The estimate of accuracy is too imprecise (i.e. very wide CI, both for sensitivity and specificity), owing to the extreme heterogeneity between study results. Moreover, too few studies and of low quality were included for this index test. This makes impossible a judgment on applicability of the index test in a real clinical setting.
CA cut-off =3 μmol/L	Sensitivity 0.94 (0.66 to 0.99) Specificity 0.82 (0.68 to 0.91)	312 (4)	30% (300 out of 1000 pregnant women with pruritus having ICP)	18 (3 to 102) women with ICP would be missed, and 126 (63 to 224) without ICP would be falsely diagnosed.	The overall accuracy found may be not applicable to a real clinical context, as most studies were at high risk of bias for patient selection and reference standard.
GCA, all cut-offs	Sensitivity 0.92 (0.65 to 0.99) Specificity 0.99 (0.06 to 1.00)	630 (6)	---	---	The estimate of accuracy is too imprecise (i.e. very wide CI, especially for specificity), owing to the extreme heterogeneity between study results. Moreover, too few studies and of low quality were included for this index test. This makes impossible a judgment on applicability of the index test in a real clinical setting.
GCA cut-off = 0.7 μmol/L	Sensitivity 0.97 (0.38 to 1.00) Specificity 0.86 (0.02 to 1.00)	333 (5)	---	---	The estimate of accuracy is too imprecise (i.e. very wide CI, both for sensitivity and specificity), owing to the extreme heterogeneity between study results. Moreover, too few studies and of low quality were included for this index test. This makes impossible a judgment on applicability of the index test in a real clinical setting.
GCA cut-off =1.5 μmol/L	Sensitivity 0.99 (0.08 to 1.00) Specificity 0.90 (0.75 to 0.97)	417 (4)	---	---	The estimate of accuracy is too imprecise (i.e. very wide CI, especially for sensitivity), owing to the extreme heterogeneity between study results. Moreover, too few studies and of low quality were included for this index test. This makes impossible a judgment on applicability of the index test in a real clinical setting.
GCA cut-off = 2 μmol/L	Sensitivity 0.99 (0.07 to 1.00) Specificity 0.97 (0.82 to 1.00)	125 (3)	---	---	The estimate of accuracy is too imprecise (i.e. very wide CI, especially for sensitivity), owing to the extreme heterogeneity between study results. Moreover, too few studies and of low quality were included for this index test. This makes impossible a judgment on applicability of the index test in a real clinical setting.
CDCA cut-off = 2	Sensitivity 0.98 (0.62 to 1.00) Specificity 0.66 (0.19 to 0.94)	312 (4)		---	The estimate of accuracy is too imprecise (i.e. very wide CI, especially for specificity), owing to the extreme heterogeneity between study results. Moreover, too few studies and of low quality were included for this index test. This makes impossible a judgment on applicability of the index test in a real clinical setting.

CDCA cut-off = 3	Sensitivity 0.75 (CI not calc) Specificity 0.94 (0.88 to 0.97)	312 (4)	---	---	The CI of sensitivity was not calculable and the CI of specificity was too wide. Hence, we cannot know the precision of the estimates obtained and their applicability in a real clinical scenario.
CA/CDCA cut-off = 1.8	Sensitivity 0.89 (0.54 to 0.98) Specificity 0.92 (0.85 to 0.96)	312 (4)	30% (300 out of 1000 pregnant women with pruritus having ICP)	33 (6 to 138) women with ICP would be missed, and 56 (28 to 105) without ICP would be falsely diagnosed	The cut-off used has been chosen among the best ones, comparing Youden indexes at multiple cut-offs applied to all studies. This may have led to biased results. Moreover, sensitivity estimate has a wide CI. This makes hard to judge the applicability the index test in a real clinical setting.
Subgroup analysis for TSBA cut-off = 10 µmol/L: timing (P = 0.027)					
Onset of symptoms	Sensitivity 0.87 (0.68 to 0.96) Specificity 0.87 (0.76 to 0.94)	839 (11)	30% (30 out of 100 pregnant women with pruritus having ICP)	39 (12 to 96) women with ICP would be missed, and 91 (42 to 168) without ICP would be falsely diagnosed	Sensitivity and specificity seem to be quite good if TSBA are tested when symptoms of ICP arise. However, the overall accuracy found may be not applicable to a real clinical context, as most studies were at high risk of bias for patient selection and reference standard.
Peak value among multiple assessments	Sensitivity 0.7 (0.24 to 0.94) Specificity 1.00 (CI not calc)	839 (11)	---	---	The CI of sensitivity was too wide and the CI of specificity was not calculable. Hence, we cannot know the precision of the estimates obtained and their applicability in a real clinical scenario.
Delivery	Sensitivity 1.00 (1.00 to 1.00) Specificity 0.87 (0.68 to 0.95)	839 (11)	30% (300 out of 1000 pregnant women with pruritus having ICP)	0 women with ICP would be missed, and 91 (35 to 224) without ICP would be falsely diagnosed	Sensitivity seems to be higher when TSBA are tested at the time of delivery, while specificity seems to be the same as when symptoms of ICP arise. However, clinicians need to diagnose ICP as soon as possible during pregnancy to monitor and strictly follow up diseased woman, in order to find possible signs of fetal distress and plan the timing of delivery. Delivery time is too late to make a diagnosis.
Sensitivity analysis for TSBA cut-off=10 µmol/L: exclusion of studies with TSBA as part of reference standard					
	Sensitivity 0.57 (0.49 to 0.65) Specificity 0.98 (0.53 to 1.00)	497 (5)	30% (300 out of 1000 pregnant women with pruritus having ICP)	129 (105 to 153) women with ICP would be missed, and 14 (0 to 329) without ICP would be falsely diagnosed	The overall accuracy of TSBA, especially sensitivity, seems to be lower when considering only studies without TSBA inclusion in the reference standard. The accuracy of the index test in a real clinical context may be similar to this. However CIs are wide, and estimates too imprecise to judge with certainty their applicability in a real clinical setting.
Sensitivity analysis for TSBA cut-off=10 µmol/L: exclusion of case-control studies					

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Sensitivity 0.57 (0.48 to 0.66) Specificity 0.92 (0.52 to 0.99)	436 (3)	30% (300 out of 1000 pregnant women with pruritus having ICP)	129 (102 to 156) women with ICP would be missed, and 56 (7 to 336) without ICP would be falsely diagnosed	The overall accuracy of TSBA, especially sensitivity, seems to be lower when excluding case-control studies. The accuracy of the index test in a real clinical context may be similar to this. However CIs are wide, and estimates too imprecise to judge with certainty their applicability in a real clinical setting.

CAUTION: The results on this table should not be interpreted in isolation from the results of the individual included studies contributing to each summary test accuracy measure. These are reported in the main body of the text of the review.

BACKGROUND

Intrahepatic cholestasis of pregnancy, also known as obstetric cholestasis, is a pregnancy-specific liver disorder, known to be possibly associated with an increased risk of severe fetal adverse events. Intrahepatic cholestasis of pregnancy was described as early as 1883 (Ahlfeld 1883), and since then 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 in pregnant women varies according to geographical location and population, as genetic and environmental factors play a role in its manifestation (Geenes 2009). Following studies from past decades, in countries of North America, Southern Europe, Asia, and Australia, the range of intrahepatic cholestasis of pregnancy was calculated to be between 0.01% and 0.1% (Reyes 1997), in some countries of South America between 1.5% and 4.0% (Reyes 1997), and in Scandinavian countries, the reported prevalence was 1.5% (Glantz 2004). Chile, Bolivia, Finland, Sweden, and Portugal are among the most affected countries in the world (Geenes 2009).

Most often the disease seems to affect women with a history of intrahepatic cholestasis during previous pregnancies (Reyes 1997) or a history of cholestasis associated with the use of oral contraceptives (Pathak 2010), with a family or personal history of biliary disease (Diken 2014), with hepatitis C viral infection (Paternoster 2002), twin pregnancies (Gonzalez 1989), or women with 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 of playing a part in causing the disease are mutations in genes which encode biliary transport proteins (Dixon 2014); or mutations in bile acid receptors (such as farnesoid X receptor) (Jacquemin 1999). Likewise, among factors suspected of having a role in causing the disease are seasonal variations (with higher prevalence reported in winter) (Brites 1998b), low selenium intake, erucic acid, increased gut absorption of bacterial endotoxins, pollutants (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 in Scandinavian countries during the last few decades (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% during the 1990s (Reyes 1997).

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

In clinical practice, presence of pruritus during the last third of pregnancy and the 'otherwise unexplained' abnormalities in the most common liver tests, seems enough to support the suspected diagnosis of intrahepatic cholestasis of pregnancy (Green-top Guideline No.43). However, owing to the nonspecific 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 never been shown. Moreover, the increased passage of bile acids through the placental barrier appears to be toxic for the foetus during intrahepatic cholestasis of pregnancy (Perez 2005; Sheik Abdul Kadir 2010), and this is why obstetricians are concerned about possible fetal adverse events. In an attempt to reduce the feared risk of stillbirth, which seems to occur most often during the last weeks of pregnancy, most clinicians choose an early delivery of the baby because of the medical condition of the mother, usually at week 36 (Puljic 2015, Lo 2015). 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).

Therapies for intrahepatic cholestasis of pregnancy so far have been empiric, and 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 interventions (Ozkan 2015).

A 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, and Yiganling, either alone, or in combination (Gurung 2013). However, the review found that UDCA seemed to improve the maternal symptom of pruritus (Gurung 2013), which is in agreement with the result of the meta-analysis by Bacq 2012. In addition, Bacq 2012 strongly suggested that UDCA was also beneficial for the fetal outcome; however, the Cochrane Review could 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 biomarker for intrahepatic cholestasis of pregnancy in current clinical practice. They are believed to be 'the best biomarker' for the disease, both diagnostic and prognostic for possible fetal adverse events, and they have been considered appropriately used in clinical practice and 'well known' by scientific literature for years. Hence, when TSBA serum concentration is found high (usually over 10 µmol/L to 14 µmol/L) in a pregnant women claiming pruritus and suspected to have intrahepatic cholestasis of pregnancy, this is enough to start an empirical treatment with UDCA and to start monitoring the woman's and her foetus's well-being. The attempt is to prevent the

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feared fetal adverse events, and decide the best timing for delivery (Diken 2014; Geenes 2014).

At first, based on these 'taken for granted' premises on TSBA, we thought of planning a systematic review to assess the accuracy of components of serum bile acid profile, especially primary bile acid concentrations (Sjovall 1966; Laatikainen 1977; Heikkinen 1983a) or total concentration of tauro-conjugated forms (Tribe 2010). They were studied as biomarkers for intrahepatic cholestasis of pregnancy some decades ago, especially in Scandinavia and South America (Sjovall 1966; Almuna 1986; Almuna 1987b). Later studies showed interest in serum bile acid profile as more sensitive laboratory techniques to assess their serum concentration became available (Sinakos 2010; Tribe 2010; Tripodi 2015), and they were hypothesised to provide more specific information than TSBA when diagnosing the disease, defining its severity, and monitoring its response to treatment (Chen 2013). Hence we wanted to find if they could be useful to improve the current clinical pathway as add-on or replacement for TSBA. However, while looking for studies to write the background, we realised that no authors had systematically reviewed TSBA accuracy before, and we started to suspect that their use as the best available test might not have been based on solid evidence. So we finally planned a protocol and then a systematic review on the diagnostic accuracy of both TSBA (the current test for intrahepatic cholestasis of pregnancy) together with serum bile acid profile, in order to assess the accuracy of these tests and their role in the diagnostic pathway.

We asked ourselves why and when TSBA have been introduced in clinical practice. Looking back to past studies on intrahepatic cholestasis of pregnancy, we found that intrahepatic cholestasis of pregnancy was also known as "recurrent jaundice of pregnancy", "icterus gravidarum", or "pruritus gravidarum" until the 1950s; and that, at first, its diagnostic criteria were mainly clinical, with commonest liver function tests performed to support clinically suspected, and exclude alternative possible, diagnoses. TSBA were introduced in intrahepatic cholestasis of pregnancy clinical pathway on the basis of some case series and case-control studies conducted mainly in Scandinavian and South America during the 1970s and 1980s (Sjovall 1966; Laatikainen 1984; Laatikainen 1977; Heikkinen 1981; Glasinovic 1982; Shaw 1982; Heikkinen 1983a; Heikkinen 1983b; Heikkinen 1983c; Lisoni 1983). They showed that the TSBA mean serum concentration, as well as cholic acid (CA), glycocholic acid (GCA), or chenodeoxycholic acid (CDCA) mean serum concentrations in some studies, were higher in women with intrahepatic cholestasis of pregnancy, when compared to healthy pregnant women. Since then, in most clinical settings, having TSBA serum concentration over a certain cut-off value became itself part of the definition of the disease. However the studies named before, despite being cited by most in support of TSBA use for the diagnosis of intrahepatic cholestasis of pregnancy, did not have an appropriate design to demonstrate TSBA diagnostic accuracy, and did not perform an appropriate statistical analysis (Colli 2014). They compared the mean serum concentrations between diseased and non-diseased pregnant women, but they did not estimate bile acids' sensitivity and specificity in detecting the disease. The publications usually reported only mean values, plus or minus two standard deviations (SD), of serum bile acid concentrations in the two groups of pregnant women, and the difference found between them was statistically significant.

TSBA use in the clinical pathway of intrahepatic cholestasis of pregnancy may have been built up to much more than a merely diagnostic role when their primary role in the pathogenesis of fetal distress was hypothesised (Laatikainen 1984). This hypothesis lead to TSBA use also as prognostic marker for intrahepatic cholestasis of pregnancy, where prognosis meant fetal outcome. Due to the very short time between onset of the disease and delivery (which means fetal outcome, and so prognosis), diagnosis and prognosis were then considered together, as two faces of the same coin. One of the most important and most cited studies following this line was published by Glantz 2004. The study showed a positive correlation between TSBA serum concentration and fetal adverse events, especially when their concentration was above 40 μmol/L, with an increase of 1% of risk per additional μmol/L. Among the 505 participants with intrahepatic cholestasis, reported by Glantz and colleagues, there were three intrauterine deaths (IUDs) of foetuses observed, which meant 0.4% of the participants (two were twin pregnancies with an IUD of one twin in both cases, one of which was found to have a tight knot of the umbilical cord; only two out of three women had TSBA above 40 μmol/L). The incidence of IUD was surprisingly similar to the one observed for the healthy pregnant women group, in contrast with higher percentages reported in previously published studies. It was assumed that the low risk observed was attributable to the 'active' management adopted (i.e. induction or caesarean section a few weeks before term). Authors concluded that active management was to be performed only with pregnant women with a level of bile salts above 40 μmol/L. However, recent studies have questioned these conclusions. The review by Henderson 2014, in line with the ROCG Green-top Guideline No.43, concluded that a correlation between IUD risk and intrahepatic cholestasis may not exist, and that there was no evidence to either support or refute active obstetric management. Moreover, a recently published prognostic systematic review by Ovadia 2019 concluded that there was an association between intrahepatic cholestasis and IUD only above 100 μmol/L of TSBA: active management should be set aside for these rare patients, while for TSBA below this serum concentration, pregnant women can probably be reassured that the risk of stillbirth is similar to that of pregnant women among the general population, provided that repeat bile acid testing is done until delivery.

Nowadays, debate on diagnosis and prognosis of intrahepatic cholestasis of pregnancy is still open, and clinicians ask for new evidence on the disease. In particular, their primary concern is to know if intrahepatic cholestasis of pregnancy determines an increased risk for fetal adverse events; and, if this is true, which monitoring methods and prognostic markers can reliably predict adverse outcomes in order to decide the best timing for delivery. However, as reliable prognosis cannot exist without reliable diagnosis, we focused our efforts on the 'first step' of diagnostic accuracy (Colli 2014): we planned a diagnostic test accuracy review instead of a prognostic accuracy review to try to summarise the best evidence available on this topic, and to provide 'state of the art' guidance over the diagnosis of intrahepatic cholestasis of pregnancy.

Target condition being diagnosed

Intrahepatic cholestasis of pregnancy is a gestation-specific liver disorder, defined as onset of pruritus, most often from the third trimester of pregnancy, associated with abnormal liver test results or raised total serum bile acids (TSBA) or both, and spontaneous

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relief after delivery in the absence of other skin or liver diseases. Severe intrahepatic cholestasis of pregnancy (previously defined by TSBA greater than 40 µmol/L (Glantz 2004)) seems to be associated with an increased proportion of adverse fetal outcomes which include the following: fetal distress; preterm birth (spontaneous or iatrogenic); meconium staining of amniotic fluid; low birth weight; respiratory distress syndrome of the baby (Glantz 2004; Zecca 2006); sudden intrauterine death (IUD), possibly due to an acute anoxic event (Sepúlveda 1991); or impaired fetal cardiomyocyte function (Williamson 2001). However this last severe and feared complication has been recently associated with the disease only when TSBA are above 100 µmol/L (Ovadia 2019).

Pruritus in the absence of skin rash, with the exception of scratching excoriations, could be the only presenting symptom of the disease.

Despite the many available tests, an accurate and early diagnosis of intrahepatic cholestasis of pregnancy can be difficult: 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.) and 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); and 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 with 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 occur within the usual 48 hours 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 diagnoses; and further investigations are mandatory (Bacq 2011).

Index test(s)

Total serum bile acids

Total serum bile acids (TSBA) are present at very low concentration (below 5 µmol/L) in the systemic circulation in normal fasting status, depending mostly on absorption from the gut (in turn dependent upon bile canalicular secretion) and hepatic extraction (Walker 2002). The usefulness of TSBA measurements in serum for a variety of liver diseases has been debated (Cravetto 1985; Azer 1997), and almost their only accepted use in current clinical practice is for the diagnosis of intrahepatic cholestasis of pregnancy (see Background).

The most often 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 certain 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, while isolated elevation of bile salts in asymptomatic pregnant women may occur. However, this finding is uncommon and stands most probably for asymptomatic hypercholanaemia of pregnancy (Tripodi 2015). This could be a reason why the high diagnostic accuracy attributed to total serum bile acids for intrahepatic cholestasis of pregnancy may be questionable (Brites 1998b; 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 (DCA), lithocholic (LCA), ursodeoxycholic acid (UDCA)), and their individual or total glyco-conjugated (G-c) and tauro-conjugated (T-c) forms (Figure 1), including ratios of some of them (CA/CDCA, G-c/T-c), measured in µmol/L. 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 still do not exist.

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Figure 1.

SERUM BILE ACIDS OF HUMAN BEINGS
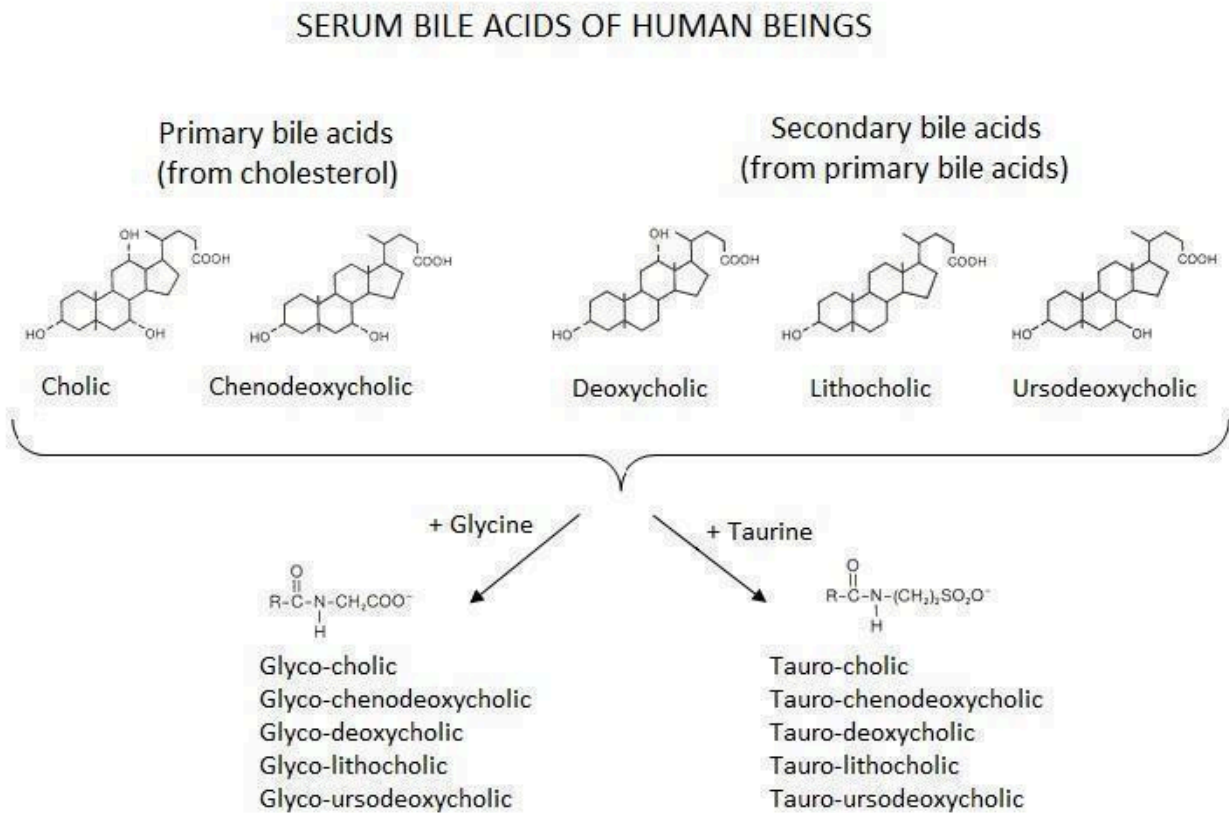
The current available laboratory methods for bile acid analysis (total or single components of serum bile acid profile) are enzyme assay, radioimmunoassay, enzyme immunoassay, and chromatographic methods such as thin-layer chromatography, gas chromatography, high performance liquid chromatography, supercritical fluid chromatography, and capillary electrophoresis, coupled with mass spectrometry, fluorometry, UV detection, or electrochemical detection methods. This is why we expected 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. Figure 2 presents a schematic overview of the current clinical pathway.

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

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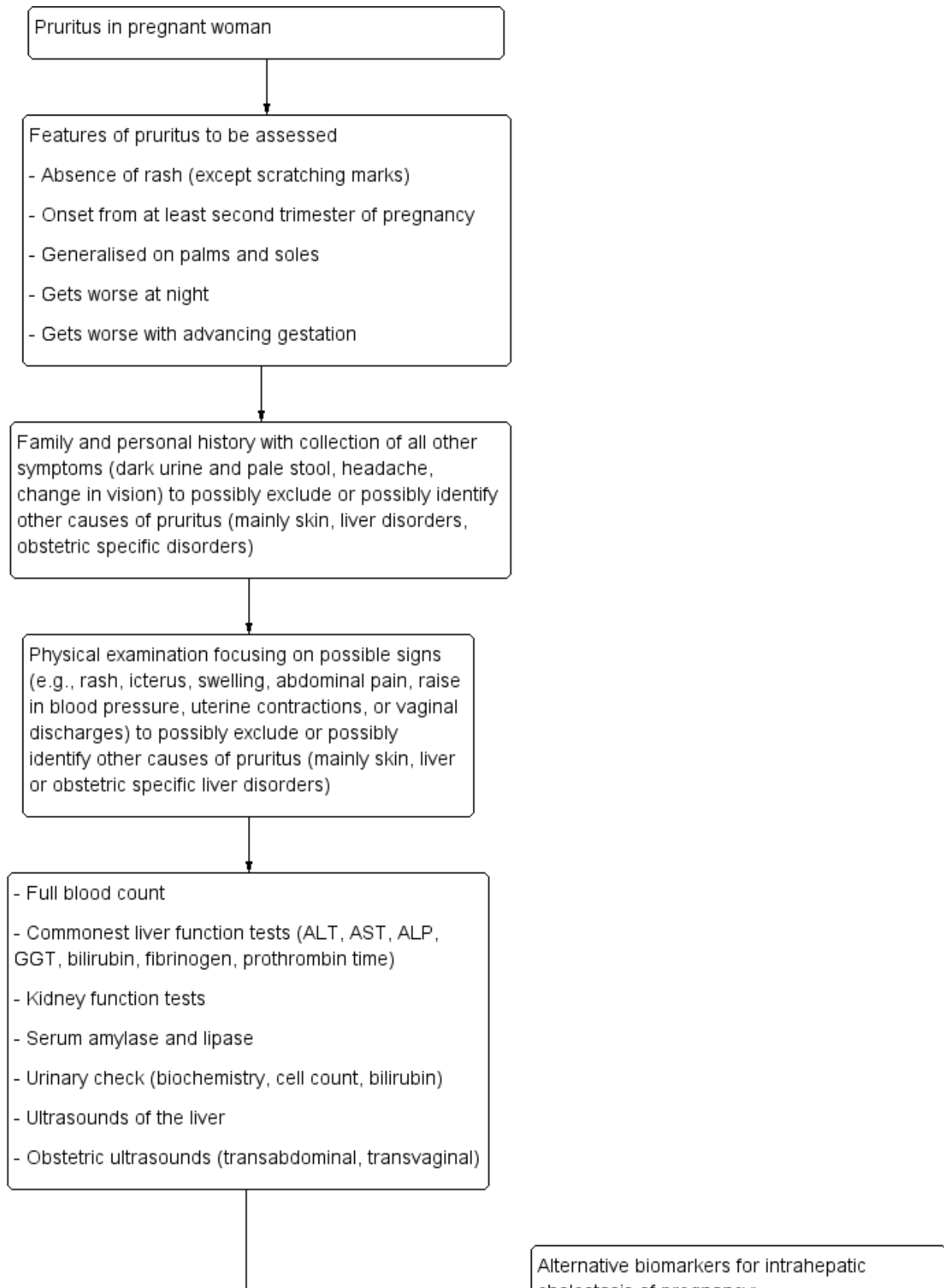
Figure 2.   (Continued)
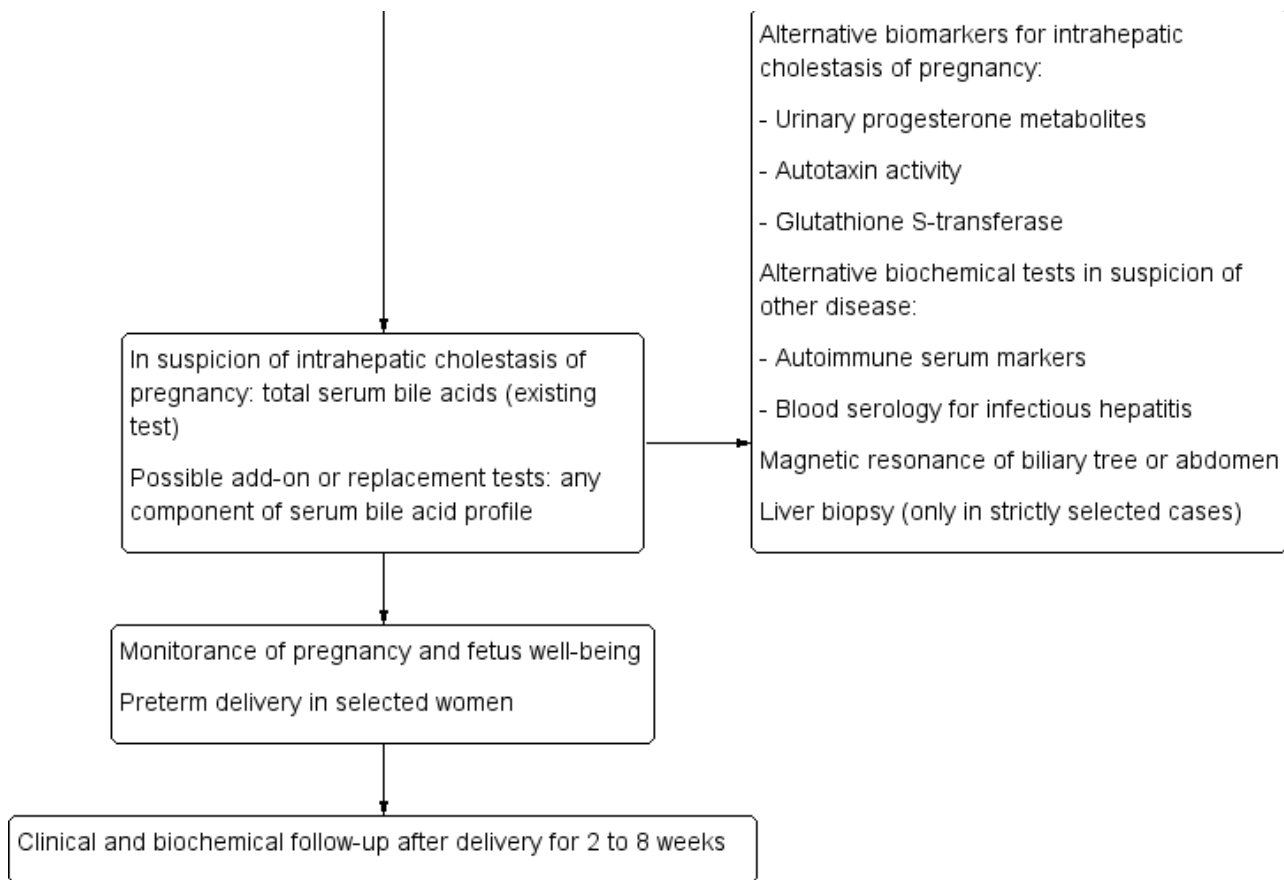
Clinical suspicion of intrahepatic cholestasis of pregnancy usually begins from the third — or at least the second — trimester of pregnancy with an onset of mild to severe pruritus, frequently generalised on the palms and soles, getting worse both at night and with advancing gestation (Kenyon 2001). In severe cases, it can also affect the ears, the eyelids, and even the oral cavity (Reyes 1997). Some studies describe instances of pruritus also from earlier stages of pregnancy (Brites 1998a; Keitel 2006; Hubschmann 2016).

After collecting all information concerning pruritus characteristics, it is mandatory to assess family and personal history, recording all other symptoms, and to carry out a physical examination to exclude or identify other plausible causes of pruritus. For example, in the presence of dark urine, pale stool, jaundice, steatorrhoea or right upper abdominal quadrant pain, alternative causes of cholestasis (e.g. bile stones of the biliary tree, tumours of hepatobiliary tract) or hepatitis of any aetiology should be suspected, as typical cholestatic symptoms in intrahepatic cholestasis of pregnancy are rare. Moreover, constitutional symptoms (insomnia, fatigue, anorexia, malaise, or abdominal pain) are not usually present (Hepburn 2008; Kondrakiene 2008; Mays 2010). Raised blood pressure, change in vision, headache, and epigastric abdominal pain may suggest pre-eclampsia or haemolysis–elevated liver enzymes–low platelet count syndrome. Any kind of rash or swelling may suggest an infectious, allergic or immunologic skin disorder, while uterine contractions, or vaginal discharges should be carefully evaluated to exclude possible obstetric complications (Diken 2014). Last but not least, alcohol problems should be excluded. A laboratory test should follow, beginning with full blood count, liver function tests, urinary check, kidney function test, amylase, and lipase. Then depending on the suspected differential diagnoses, specific tests should be performed. 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, and 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 kind of hepatotropic viral agents such as hepatitis A, B, C, D, or E viruses, cytomegalovirus, and Epstein-Barr virus. Also iron balance tests (ferritin, transferrin, saturation of transferrin) and copper metabolism biomarkers should be considered. Total serum bile acids are tested when intrahepatic cholestasis of pregnancy is suspected.

Among the imaging techniques, ultrasound examination of the abdomen focusing on the liver and biliary tree should be performed; and if it cannot rule out other cholestatic diseases, then magnetic resonance 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 indicated for the diagnosis of intrahepatic cholestasis of pregnancy because of the risks

associated with the procedure; but if performed, it may reveal pure cholestasis, with bile plugs sometimes visible in the hepatocytes and canaliculi (Bacq 2014).

An ideal method to predict fetal outcome does not exist, but obstetric examination with ultrasounds could help in ruling out high risk conditions of pregnancy and in assessing the well-being of the foetus, while a 'non-stress test' through cardiotocography (CTG) and biophysical profile (BPP) could also provide information about the well-being of the baby at the time of the investigation (Diken 2014). If any signs of fetal distress are noticed, or if total serum bile acid shows an increment without benefit from UDCA therapy, the obstetrician may decide for an early delivery of the baby to prevent the feared fetal adverse events which seem to be related with intrahepatic cholestasis of pregnancy.

Prior test(s)

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 discussed (Mullally 2002). Among the most common liver tests are serum aminotransferases (altered in up to 60% of women, but with lower values when compared to other aetiologies of liver disease such as viral hepatitis) (Diken 2014); gamma-glutamyl transpeptidase (raised in less than one-third of women with intrahepatic cholestasis of pregnancy) (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 when compared to other cholestatic diseases) (Reyes 1992); fibrinogen and prothrombin time. The prothrombin can be altered in case of severe liver dysfunction or vitamin K malabsorption due to cholestasis, leading to an increased risk of postpartum bleeding, but this is a very rare finding 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 taken 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).

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) (Bossuyt 2006).

Total serum bile acids (TSBA) are the existing test for the diagnosis of intrahepatic cholestasis of pregnancy. They are usually assessed after the most common liver tests described above when intrahepatic cholestasis of pregnancy is suspected. However, even if they are the existent test for intrahepatic cholestasis of pregnancy, a systematic review of their diagnostic accuracy has

never been done, so we wanted first to assess their accuracy before looking for a test which may replace them or be added (add-on).

Components of serum bile acid profile (cholic acid (CA), glycocholic acid (GCA), chenodeoxycholic acid (CDCA), cholic/chenodeoxycholic acid ratio (CA/CDCA), deoxycholic acid (DCA), lithocholic acid (LCA), ursodeoxycholic acid (UDCA), 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)) could be considered as add-on tests after TSBA. We calculated the overall diagnostic accuracy of some we wanted to consider as a replacement test of TSBA or add-on tests after TSBA to improve the current clinical pathway.

Alternative test(s)

As alternative tests we can consider those that can be used to assess intrahepatic cholestasis of pregnancy, and all other serum and urinary biochemical tests or imaging techniques which can lead to exclusion of possible differential diagnosis (see Clinical pathway).

However, we also found some biomarker tests which were studied for their accuracy in diagnosing intrahepatic cholestasis of pregnancy, but these biomarker tests were mostly performed in a research setting. Among them are urinary progesterone metabolites, serum autotaxin activity, and glutathione S-transferase. Urinary progesterone sulphated metabolites were found to be directly related to the pathogenesis of the disease and were studied for the diagnosis of intrahepatic cholestasis of pregnancy as well as for monitoring response to its 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 was shown to rapidly increase in case 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 2008).

Rationale

Intrahepatic cholestasis of pregnancy is considered in clinical practice a high-risk condition in pregnant women, mainly because of the increased risk of fetal adverse events. Currently, total serum bile acids are the most used diagnostic and prognostic marker for the disease, while serum bile acid profile components are less commonly used. A systematic review of diagnostic test accuracy of total serum bile acids and serum bile acid profile components has never been published. Thus, to assess the accuracy of total serum bile acids and serum bile acid profile components, independently or in combination, and to define which index test (or combination of index tests) could be better for use, may help to improve the current clinical pathway and clinicians' approach to the disease, leading to a direct benefit on the outcomes of both pregnant women and their babies. After that, a prognostic accuracy review to assess the reliability of our index tests as prognostic markers for the disease, could become feasible.

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OBJECTIVES

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

Secondary objectives

To define the optimal cut-off values for components of serum bile acid profile; to investigate possible sources of heterogeneity (see below in Investigations of heterogeneity paragraph).

METHODS

Criteria for considering studies for this review

Types of studies

We included studies that evaluated the diagnostic accuracy of the index tests for the diagnosis of intrahepatic cholestasis of pregnancy and used the proper reference standards (see below), irrespective of publication status, language, and prospective or retrospective design. We considered studies of cross-sectional design including participants with clinical suspicion of intrahepatic cholestasis of pregnancy, as well as studies of case-control design that compared people with known intrahepatic cholestasis of pregnancy to matched control (pregnant women without evidence of intrahepatic cholestasis of pregnancy participants).

Participants

Pregnant women of any age, recruited in any clinical setting. They should have been tested by at least one of the index tests and they should have undergone the reference standard (see below).

In cross-sectional studies, participants should have been pregnant women with suspicion of having the target disease (e.g. presenting with new onset of pruritus during pregnancy).

In case-control studies, the case group should have included pregnant women in which intrahepatic cholestasis of pregnancy had been confirmed through the reference standard (see below), while the control group should have comprised asymptomatic or symptomatic pregnant women in which the target condition had been ruled out with clinical evaluation and biochemical tests.

Index tests

The index tests we considered are total serum bile acids (TSBA) and the following components of serum bile acid profile.

- Cholic acid (CA)
- Glycocholic acid (GCA)
- Chenodeoxycholic acid (CDCA)
- Cholic/chenodeoxycholic acid ratio (CA/CDCA)
- Deoxycholic acid (DCA)
- Lithocholic acid (LCA)
- Ursodeoxycholic acid (UDCA)
- 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)

The measurements of these index tests are performed in laboratories with different automated techniques (see Background). TSBA are commonly measured by almost all clinical laboratories, while techniques to measure components of serum bile acid profile are currently available only in clinical research settings.

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

The obstetric clinical evaluation in which the follow-up after delivery is included. The clinical evaluation is the final judgment of the clinician who takes into account clinical assessment of the signs and symptoms suggestive for intrahepatic cholestasis of pregnancy and the presence of any otherwise unexplained, persistent abnormalities of AST, ALT, or bilirubin levels until delivery. The follow-up after delivery is the assessment of spontaneous resolution of symptoms and normalisation of liver tests (i.e. liver test measurements below upper normal limits) within at least 48 hours or eight weeks at most.

For the final diagnosis, the obstetric evaluation could be enough when differential diagnoses can be easily ruled out. For difficult clinical cases, an evaluation and consensus with an hepatologist could be useful.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Hepato-Biliary Group Controlled Trials Register (maintained and searched internally by the CHBG Information Specialist via the Cochrane Register of Studies Web; 6 May 2019), the Cochrane Hepato-Biliary Group Diagnostic Test Accuracy Studies Register (maintained and searched internally by the CHBG Information Specialist via the Cochrane Register of Studies Web; 6 May 2019), the Cochrane Library (2019, Issue 5), MEDLINE Ovid (1946 to 6 May 2019), Embase Ovid (1974 to 6 May 2019), Science Citation Index Expanded (Web of Science, 1900 to 6 May), Conference Proceedings Citation Index – Science (Web of Science; 1990 to 6 May 2019), BIOSIS (Web of Science; 1969 to 6 May 2019), and CINAHL (EBSCO*host;* 1981 to 6 May 2019) (Royle 2003)**.**

We searched Chinese literature through Chinese CKNI (1979 to May 2019) and VIP (1989 to May 2019) with the help of Maoling Wei from the Chinese Cochrane Centre.

As the highest prevalence of the disease is observed in Chile, on contacting some South American expert authors we were advised to search thoroughly two local databases: Literatura Latino-Americana e do Caribe em Ciências da Saúde [Literature in the Health Sciences in Latin America and the Caribbean] (LILACS) and Scientific Electronic Library Online (SciELO) (both searched 6 May 2019).

We also searched through some field-databases suggested by the Royal College of Obstetricians and Gynaecologists: the Evidence Search: Health and Social Care by NICE; the World Health

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Organization (WHO) Reproductive Health Library (RHL); and the Turning Research into Practice database (TRIP) (6 May 2019).

We applied no restrictions with regard to language or document type.

We give the search strategies with the time spans of the searches in Appendix 1.

Searching other resources

We identified 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 'intrahepatic cholestasis of pregnancy support' web site (www.icpsupport.org/papers.shtml), in order to identify other potentially relevant studies for inclusion in our review.

We searched also 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 searched on-line trial registries such as 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.

Data collection and analysis

We followed the available guidelines provided in the *Cochrane Diagnostic Reviewer's Handbook* (DTA Handbook 2010).

Selection of studies

Two authors (CM, TS) independently conducted the first selection of studies by reading titles or abstracts or both of the identified studies. The two authors independently reviewed the full texts for eligibility, assessing the fulfilment of the inclusion criteria. During this second selection stage, when the two authors found multiple publications of one study fulfilling the inclusion criteria, they grouped them together and they screened these publications for complementary data or checked them for discrepancies. When in doubt, the review authors emailed study authors to ensure that publications referred to the same study and to check the correctness of data.

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

Data extraction and management

Two authors (CN, TS) independently completed data extraction from each included study. They solved disagreements by discussion or by consulting a third author (CG, GC, or DN).

They retrieved the following study data.

- General information: title, journal, year, publication status, study design (cross-sectional or case-control, prospective or retrospective, single centre or multicentre), time span considered.

- Total number of women screened for inclusion in the study, number of pregnant women included, and prevalence of the disease in the considered population.
- Baseline characteristics: age, ethnicity, country, if pregnancies were twin or singleton, week of pregnancy in which the index tests were performed, disease severity if reported, and concurrent medications used.
- If most common liver tests were performed, and their findings.
- Index tests (total serum bile acids or any component of serum bile acid profile): technique used for the measurement, fasting or postprandial status of women while the test was performed, predefined cut-off values for the diagnosis if reported.
- 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, true negative, false positive, and false negative 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 authors summarised data from each study in two-by-two tables (false positive (FP), false negative (FN), true positive (TP), true negative (TN)) and entered the data into Review Manager 5 (Review Manager 2014).

Missing data

When information on any of the FP, FN, TP, or TN diagnostic test values were missing, we attempted to contact the authors of the included studies in order to obtain missing information. We also contacted authors if other types of information needed for this review was missing, especially when the publication was in the form of an abstract or poster presentation. We used Excel and Review Manager 5 to add data required for statistical analyses (Review Manager 2014).

We contacted primary authors for missing data by e-mail. In absence of a reply, we sent a second e-mail a week after, and when possible we tried to contact the study authors by telephone. We acknowledged study authors for providing missing data, and we created references to unpublished studies when such study data were obtained through personal communication (see notes under each study in Characteristics of included studies).

We excluded the studies when we could not 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 independently assessed the risk of bias of the included studies using four QUADAS-2 domains (Whiting 2011). A third review author (GC) checked the extracted information and the risk of bias assessments. We resolved disagreements by discussion or by consulting a fourth review author (CG or DN). We contacted study authors if information on methodology was lacking in order to assess correctly the risk of bias of the studies.

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

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

Statistical analysis and data synthesis

We carried out the analyses following guidelines in Chapter 10 (Analysing and Presenting Results) of the *Cochrane Diagnostic Reviewer's Handbook* (DTA Handbook 2010). We used Review Manager 5 software for analyses and forest plots (Review Manager 2014).

We built two-by-two tables for each primary study and for all the index tests considered. We estimated sensitivity and specificity, with their 95% confidence intervals (CI). We presented data in coupled forest plots, showing sensitivities and specificities of each study, with their 95% CI. In forest plots, studies were ordered according to study authors' names or, when heterogeneity analysis was performed, according to the source of heterogeneity.

We plotted the studies in summary Receiver Operating Characteristic (ROC) curves when studies with different cut-offs were considered together, or we represented the studies as circles in the ROC space when the studies included in the analysis had the same cut-off, reporting sensitivity against specificity. The size of circles in the ROC space are proportional to the number of participants included in the study. We represented the 95% confidence regions of mean specificity and sensitivity as areas surrounding the circles.

When individual participant data were available, or when studies used a common cut-off, we attempted to meta-analyse data at different cut-offs and, when possible, to obtain multiple estimates of accuracy for the same index tests.

When the included primary studies reported accuracy data using different cut-off values, we adopted the hierarchical summary ROC model (HSROC) to pool data and to estimate a summary ROC (SROC) curve. When a sufficient number of primary studies reported data using a common cut-off value, we performed meta-analyses using the bivariate model, and we provided the estimate of the summary operating point (mean sensitivity and mean specificity) at that cut-off value.

For primary studies that reported accuracy results for more than one cut-off point, we reported sensitivities and specificities for all of the cut-off points, but we used a single cut-off point for each study in HSROC or bivariate model analysis. We based our choice on the cut-off value most commonly reported, or in case a study did not report data on the most commonly used cut-off, we based our choice on the value corresponding to the maximum of the Youden's index (sensitivity + specificity − 1),

We made direct and indirect comparisons between the considered index tests by adding a covariate term for the index test to the bivariate or HSROC model, as appropriate. We assessed the significance of differences in test accuracy by using the log-likelihood ratio test for comparison of models with and without the index test covariate term. We considered P values less than 0.05, two-sided, as statistically significant.

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

Investigations of heterogeneity

For the eleven studies assessing TSBA diagnostic accuracy with cut-off equal to 10 µmol/L, we investigated the following sources of heterogeneity.

- Laboratory technique used to measure the index test
- Therapy (if study patients underwent therapy with UDCA or not)
- Timing of measurement of index test (onset of symptoms, peak values among multiple assessments during pregnancy, immediately before delivery)

We investigated heterogeneity first by visual inspection of the paired forest plots of sensitivities and specificities for each index test. Then, we performed a formal analysis by adding covariates to the bivariate or HSROC model.

Sensitivity analyses

We performed the following sensitivity analysis.

- Excluding all studies with case-control design
- Excluding studies in which the index test was part of the reference standard

Assessment of reporting bias

We decided not to assess publication bias.

'Summary of findings' table

To construct a 'Summary of findings' table for presenting the key findings of our review, we used the approach developed by the Cochrane GRADEing group (formerly, the Cochrane Applicability and Recommendations Methods Group) which is in conformity with QUADAS 2 (see Chapter 11, DTA Handbook 2013; Whiting 2011).

R E S U L T S

Results of the search

We identified a total of 5073 references. We identified 3511 references through electronic searches of the Cochrane Hepato-Biliary Group Controlled Trials Register (n = 22) and the Cochrane Hepato-Biliary Group Diagnostic Test Accuracy Studies Register (n = 0), the Cochrane Library (n = 115), MEDLINE Ovid (n = 770), Embase Ovid (n = 1409), Science Citation Index Expanded and Conference Proceedings Citation Index – Science (n = 592), BIOSIS Previews (n = 539), and CINAHL (EBSCO) (n = 64). We also identified 1043 references through the two Chinese databases CNKI and VIP, but we only considered nine were relevant; these were sent to us by the Chinese colleague who performed the search, and 242 references through electronic searches of the two South American databases LILACS and SciELO. In addition, we identified 277 references through electronic search of Evidence search: Health and Social Care, RHL, TRIP, and handsearching ProQuest Dissertations & Thesis Database, Index to Theses in Great Britain and Ireland, OpenSIGLE, NTIS, on-line trials registers, conference proceedings and references taken from other publications and

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found to be potentially relevant. After exclusion of 1324 duplicates, 2715 publications were screened for inclusion. We excluded 2644 publications at a first selection, all by reading the title and abstract; and 259 publications by reading also the full text. Seventy-one full-text articles seemed to fulfil the inclusion criteria, and we finally

excluded 55, most of them only after contacting study authors in order to bring together more information.

We included 16 relevant studies in this systematic review. Figure 3 presents a schematic overview of the study selection process.

Figure 3. Study selection flow diagram.
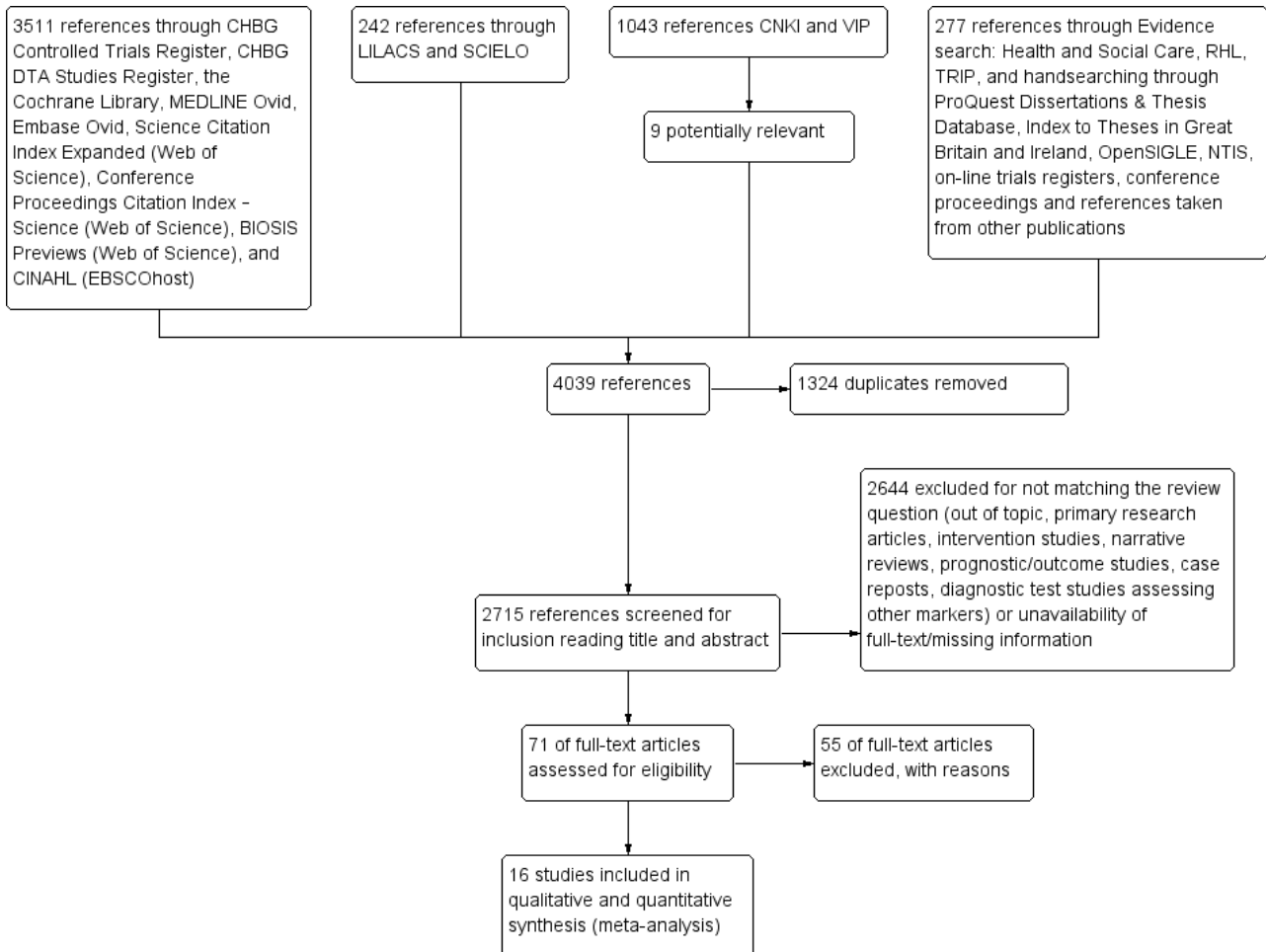
References of included studies, ordered by study ID, are given in Included studies.

Additional Table 1 provides the main published or unpublished (given by email from study authors) characteristics of the included studies. For more detailed information on each study's characteristics, comprising the information obtained by email from authors, see Characteristics of included studies.

We retrieved individual participant data (marked with **"*"** in Additional Table 1) of nine included studies from their authors by email personal correspondence, while two studies already contained individual participant data in the publication. This allowed us to consider also the index tests performed by the study authors but not published, and to calculate the diagnostic accuracy of the index tests performed in these studies at cut-offs different from the published ones; (for more detailed information on unpublished data, as well as on how diagnostic accuracy of unpublished index tests was calculated, see Characteristics of included studies). This is the reason why we finally had 13 studies

assessing the diagnostic accuracy of TSBA, 4 studies of CA and CDCA, 4 studies of CA/CDCA, and 6 studies of GCA.

Some of the studies assessing the diagnostic accuracy of the components of serum bile acid profile analysed in our review assessed also the diagnostic accuracy of LCA, DCA, UDCA, G-c, T-c, and G-c/T-c. They reported that T-c acids increased in the third trimester of pregnancy in women with intrahepatic cholestasis of pregnancy, and that G-c/T-c of less than 1.0 μmol/L had high diagnostic accuracy. Another finding was that LCA was higher in serum of women with intrahepatic cholestasis of pregnancy, while UDCA was lower (Brites 1998b; Brites 1998c; Tripodi 2015). However, as the number of studies assessing the diagnostic accuracy of LCA, DCA, UDCA, G-c, T-c, and G-c/T-c was three or fewer for each, we found it useless to meta-analyse their data, even when taking into account the studies for which we had individual participant data, owing to statistical limitations and the high risk of random errors.

We could not analyse the accuracy of combinations of the index tests, defined in our protocol as TSBA plus any component of serum bile acid profile, as none of the included studies measured these combinations.

For our analysis of TSBA, irrespective of the cut-off values used to assess the TSBA accuracy, we had data from 1645 participants; and with TSBA serum concentration of 10 µmol/L as diagnostic cut-off value, we had data from 839 participants. Thanks to the availability of individual participant data for all studies assessing CA, GCA, CDCA, and CA/CDCA, the number of participants for each test was the same for every cut-off considered: 312 participants for CA, 630 for GCA, 312 for CDCA, and 312 for CA/CDCA.

Methodological quality of included studies

Figure 4 shows the risk of bias for each study across each QUADAS-2 domain and Figure 5 shows the overall risk of bias assessment for all included studies across each QUADAS-2 domain.

Figure 4. Risk of bias and applicability concerns summary: review authors' (CM and TS) judgements about each domain for each included study. N.B. The empty cells stand for the test, not performed in the study.

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Figure 4. (Continued)

Figure 5. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies
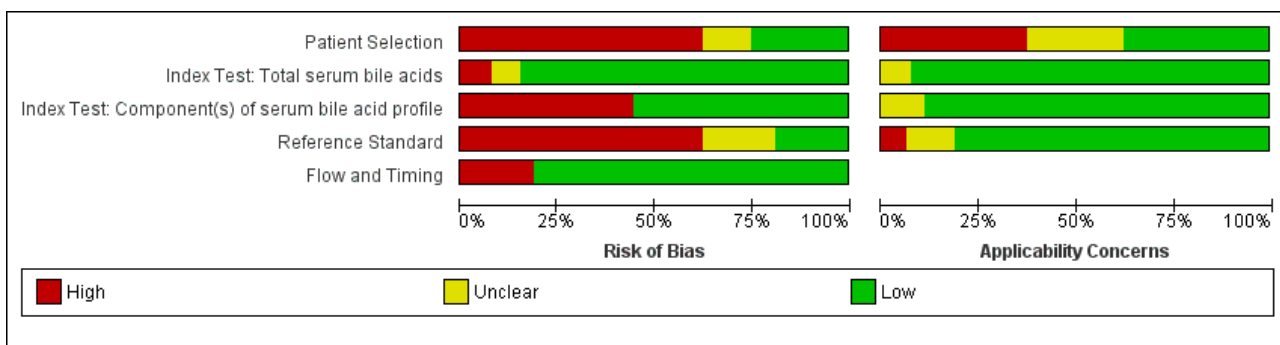
We assessed only one study at low risk of bias in all four QUADAS-2 domains (Huang 2009). The most biased domains were the patient-sampling domain and the reference standard domain. We judged the patient-sampling domain at high risk of bias in most cases because of the case-control design, as it excludes all 'difficult to diagnose' patients. We judged the reference standard domain at high risk of bias in most studies because of the inclusion of the index test TSBA in its definition. For applicability concerns, most studies had a high concern regarding patient selection, because the characteristics of selected participants (exclusion of 'difficult to diagnose' patients from cases group; absolutely asymptomatic and healthy pregnant women, often in a very early stage of pregnancy in control groups) excluded them as representative for clinical practice. Only five studies were representative for all domains (Laatikainen 1984; Almuna 1986; Roger 1994; Jiang 2012; Lang 2012).

For more detailed information on each study's quality assessment according to QUADAS-2, see Characteristics of included studies.

Findings

In this review, we estimated the overall accuracy of TSBA and some components of serum bile acid profile (CA, GCA, CDCA and CA/CDCA) for the diagnosis of intrahepatic cholestasis of pregnancy. We did not perform the analysis of the remaining components of serum bile acid profile (i.e. LCA, DCA, UDCA, G-c, T-c, G-c/T-c) as there were too few data available.

Total serum bile acids (TSBA)

TSBA was the index test with the highest number of studies assessing its accuracy (Figure 6). The commonest cut-off value used by studies was 10 µmol/L. Hence, after a first analysis considering all 13 studies (Figure 7), we analysed together only the 11 studies for which estimates of accuracy were available for a cut-off of 10

µmol/L (Figure 8). Considering only studies using a cut-off of 10 µmol/L, or those which it was possible to apply this cut-off, we found the overall sensitivity and specificity estimated for TSBA to be respectively 0.91 (95% CI 0.72 to 0.98) and 0.93 (95% CI 0.81 to 0.97) (Figure 9).

Figure 6. Forest plot of total serum bile acids (TSBA) (all studies) for the diagnosis of intrahepatic cholestasis of pregnancy

Study	TP	FP	FN	TN	Cut-off	ICP	Patient selection	Sensitivity (95% CI)	Specificity (95% CI)
Brites 1998b	39	1	0	37	10.0	Clinical+ laboratory+TSBA/ with FU	Case-control healthy	1.00 [0.91, 1.00]	0.97 [0.86, 1.00]
Brites 1998c	8	0	1	5	10.0	Clinical+ laboratory+TSBA/ with FU	Case-control healthy	0.89 [0.52, 1.00]	1.00 [0.48, 1.00]
Gonzalez 1989	13	8	0	41	10.0	Clinical+ laboratory+TSBA/ with FU	All	1.00 [0.75, 1.00]	0.84 [0.70, 0.93]
Guducu 2013	14	4	0	15	10.0	Clinical+ laboratory+TSBA/ with FU	Case-control healthy	1.00 [0.77, 1.00]	0.79 [0.54, 0.94]
Huang 2009	34	33	21	105	10.0	Clinical+laboratory/ with FU	Suspected	0.62 [0.48, 0.75]	0.76 [0.68, 0.83]
Jiang 2012	247	42	103	308	11.0	Clinical+ laboratory+TSBA/ with FU	Case-control healthy	0.71 [0.65, 0.75]	0.88 [0.84, 0.91]
Kowalska-Kanka 2013	28	5	0	40	11.0	Clinical+ laboratory+TSBA/ with FU	Case-control healthy	1.00 [0.88, 1.00]	0.89 [0.76, 0.96]
Laatikainen 1984	58	0	59	60	10.0	Clinical+laboratory/ with FU	Suspected	0.50 [0.40, 0.59]	1.00 [0.94, 1.00]
Lang 2012	22	4	18	22	14.0	Clinical+laboratory/ with FU	Suspected	0.55 [0.38, 0.71]	0.85 [0.65, 0.96]
Roger 1994	12	1	5	16	6.0	Only clinical+FU	Case-control healthy	0.71 [0.44, 0.90]	0.94 [0.71, 1.00]
Sjovall 1966	5	0	1	22	10.0	Only clinical+FU	Case-control healthy	0.83 [0.36, 1.00]	1.00 [0.85, 1.00]
Sun 2011	48	4	7	46	20.0	Clinical+laboratory/ with FU	Case-control healthy	0.87 [0.76, 0.95]	0.92 [0.81, 0.98]
Tripodi 2015	41	10	4	28	10.0	Clinical+ laboratory+TSBA/ with FU	Case-control healthy	0.91 [0.79, 0.98]	0.74 [0.57, 0.87]

Figure 7. Summary receiver operating characteristic (ROC) plot of total serum bile acids (TSBA) (all studies) for the diagnosis of intrahepatic cholestasis of pregnancy. Statistical method used: HSROC (hierarchical summary ROC) model.

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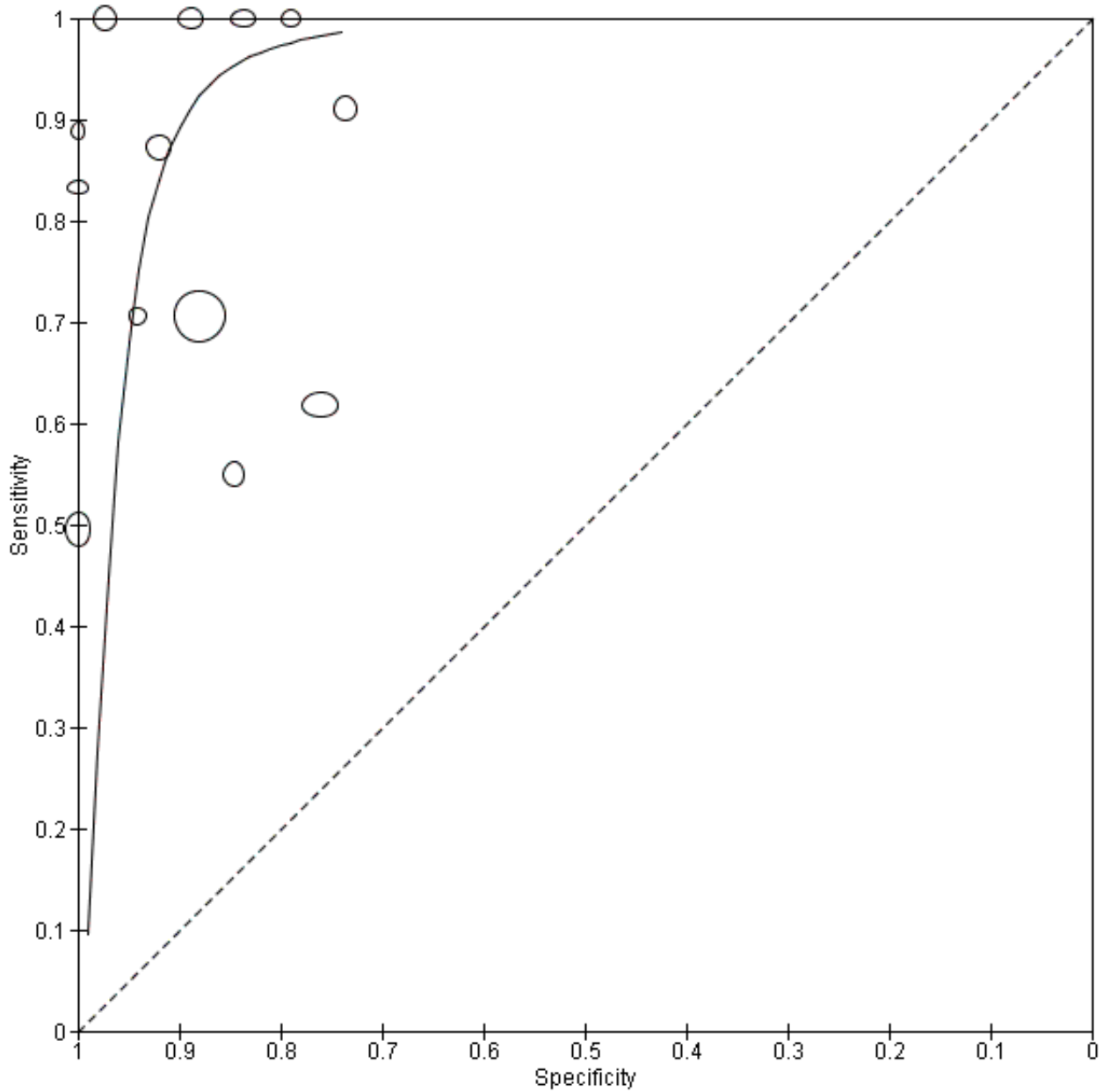
Figure 8. Forest plot of total serum bile acids (TSBA) with cut-off = 10 μmol/L for the diagnosis of intrahepatic cholestasis of pregnancy

Study	TP	FP	FN	TN	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)
Brites 1998b	39	1	0	37	10.0	1.00 [0.91, 1.00]	0.97 [0.86, 1.00]
Brites 1998c	8	0	1	5	10.0	0.89 [0.52, 1.00]	1.00 [0.48, 1.00]
Gonzalez 1989	13	8	0	41	10.0	1.00 [0.75, 1.00]	0.84 [0.70, 0.93]
Guducu 2013	14	4	0	15	10.0	1.00 [0.77, 1.00]	0.79 [0.54, 0.94]
Huang 2009	34	33	21	105	10.0	0.62 [0.48, 0.75]	0.76 [0.68, 0.83]
Kowalska-Kanka 2013	28	5	0	40	10.0	1.00 [0.88, 1.00]	0.89 [0.76, 0.96]
Laatikainen 1984	58	0	59	60	10.0	0.50 [0.40, 0.59]	1.00 [0.94, 1.00]
Lang 2012	24	6	15	20	10.0	0.62 [0.45, 0.77]	0.77 [0.56, 0.91]
Roger 1994	11	0	6	17	10.0	0.65 [0.38, 0.86]	1.00 [0.80, 1.00]
Sjovall 1966	5	0	1	22	10.0	0.83 [0.36, 1.00]	1.00 [0.85, 1.00]
Tripodi 2015	41	10	4	28	10.0	0.91 [0.79, 0.98]	0.74 [0.57, 0.87]

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Figure 9. Summary receiver operating characteristic (ROC) plot of of total serum bile acids (TSBA) with cut-off = 10 µmol/L for the diagnosis of intrahepatic cholestasis of pregnancy. Statistical method used: bivariate model.
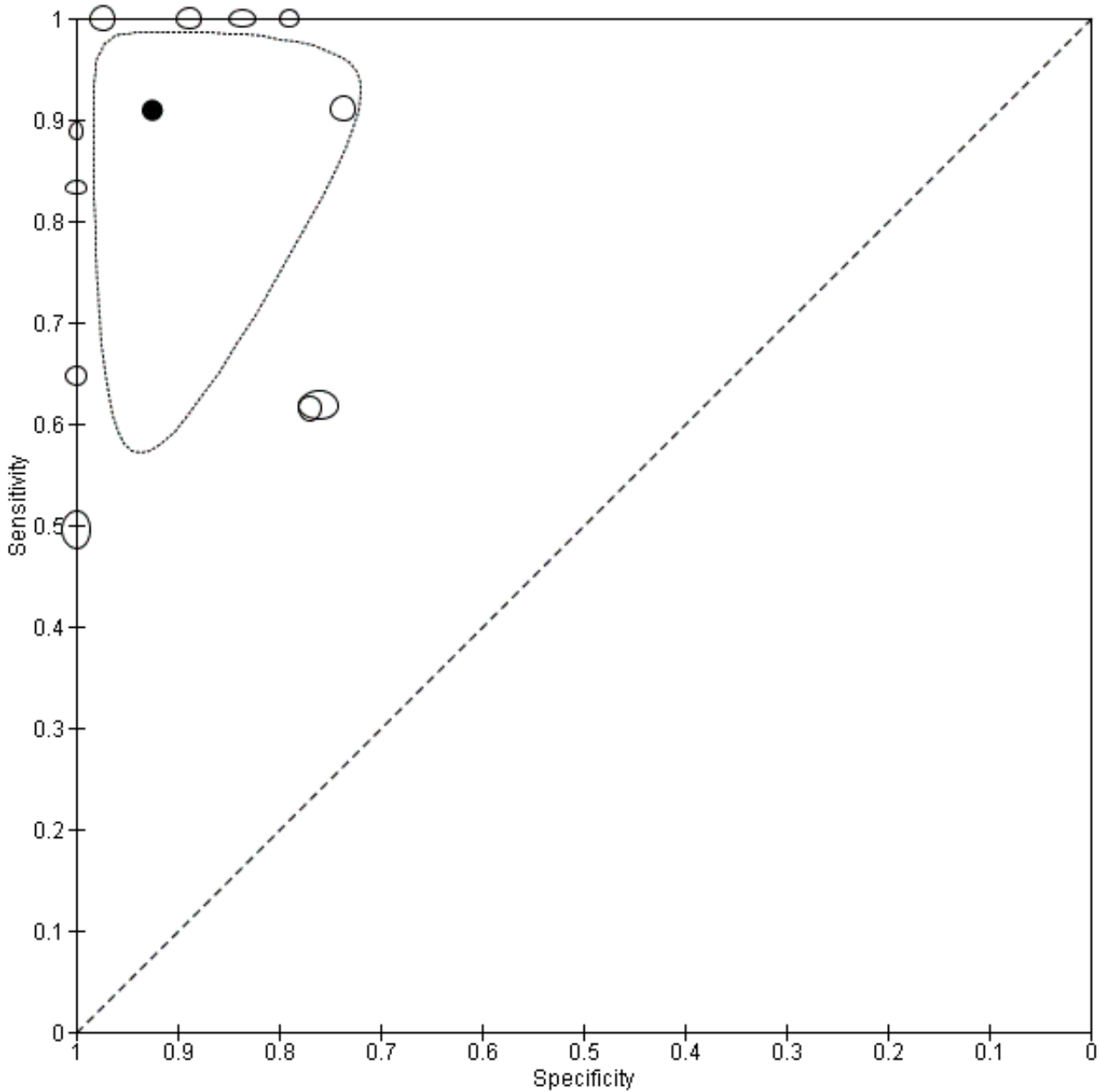
Glycocholic acid (GCA)

At first we considered all six studies together when estimating GCA accuracy (Figure 10, Figure 11). Then we also estimated GCA accuracy at the three most reported cut-offs: 0.7 µmol/l (5 studies), 1.5 µmol/L (4 studies), and 2 µmol/L (3 studies).

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Figure 10.   Forest plot of glycocholic acid (GCA) (all studies) for the diagnosis of intrahepatic cholestasis of pregnancy

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Almuna 1986	23	0	32	136	0.42 [0.29, 0.56]	1.00 [0.97, 1.00]
Almuna 1987b	8	0	0	14	1.00 [0.63, 1.00]	1.00 [0.77, 1.00]
Brites 1998b	38	0	1	38	0.97 [0.87, 1.00]	1.00 [0.91, 1.00]
Brites 1998c	8	0	1	5	0.89 [0.52, 1.00]	1.00 [0.48, 1.00]
Lunzer 1986	15	16	0	266	1.00 [0.78, 1.00]	0.94 [0.91, 0.97]
Roger 1994	9	8	3	9	0.75 [0.43, 0.95]	0.53 [0.28, 0.77]

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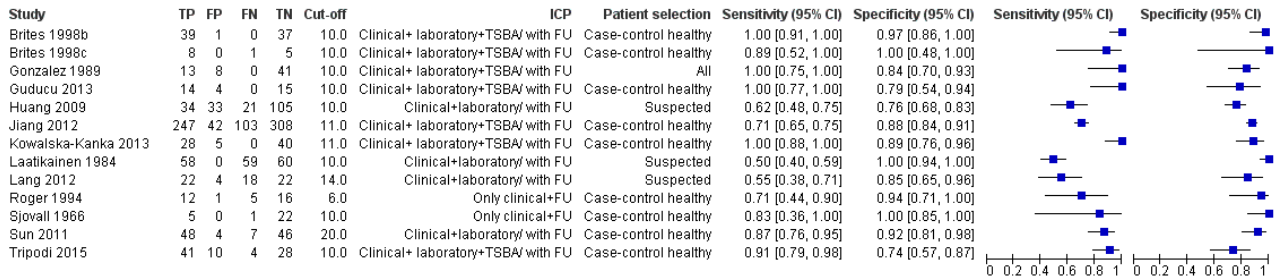**Better health.**

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Figure 11.   Summary receiver operating characteristic (ROC) plot of glycocholic acid (GCA) (all studies) for the diagnosis of intrahepatic cholestasis of pregnancy. Statistical method used: HSROC (hierarchical summary ROC) model.
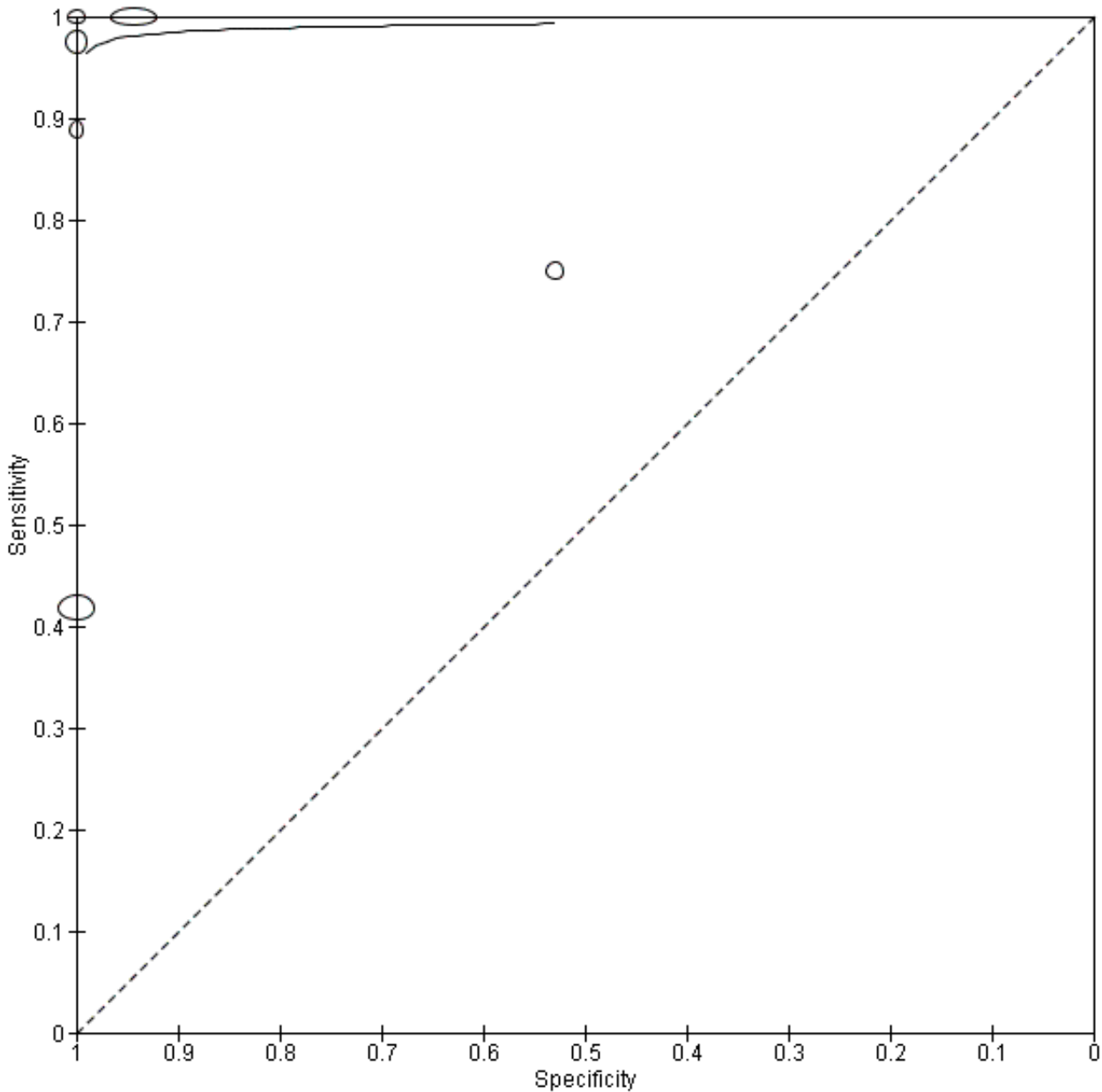
The overall sensitivity was 0.92 (95% CI 0.65 to 0.99) and the overall specificity was 0.99 (95% CI 0.06 to 1.00), considering all studies. When considering a cut-off of 0.7 μmol/L, they were 0.97 (95% CI 0.38 to 1.00) and 0.86 (95% CI 0.02 to 1.00) respectively; when the cut-off was 1.5 μmol/L, they were 0.99 (95% CI 0.08 to 1.00) and 0.90 (95% CI 0.75 to 0.97) respectively; and when the cut-off 2.0 μmol/L, they were 0.99 (95% CI 0.07 to 1.00) and 0.97 (95% CI 0.82 to 1.00) respectively.

Cholic acid (CA)

Four included studies assessed the diagnostic accuracy of CA. Having obtained individual participant data of all four, we were able to calculate specificity and sensitivity for each study at multiple cut-offs (2, 3, 4, and 5 μmol/l) (Figure 12). However, the only cut-off values for which it was possible to estimate the overall accuracy and its 95% CI were 2 μmol/L and 3 μmol/l: CA with a cut-off of 2 μmol/L had a sensitivity of 0.99 (95% CI 0.33 to 1.00) and a specificity of 0.61 (95% CI 0.23 to 0.89), while CA with a cut-off of 3 μmol/L had a sensitivity of 0.94 (95% CI 0.66 to 0.99) and a specificity of 0.82 (95% CI 0.68 to 0.91). For a cut-off of 4 μmol/L and 5 μmol/L, we were not able to estimate the overall sensitivity and specificity.

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Figure 12. Forest plots of cholic acid (CA) with different cut-offs for the diagnosis of intrahepatic cholestasis of pregnancy: a) cut-off 2 µmol/L; b) cut-off = 3 µmol/L; c) cut-off = 4 µmol/L; d) cut-off = 5 µmol/L
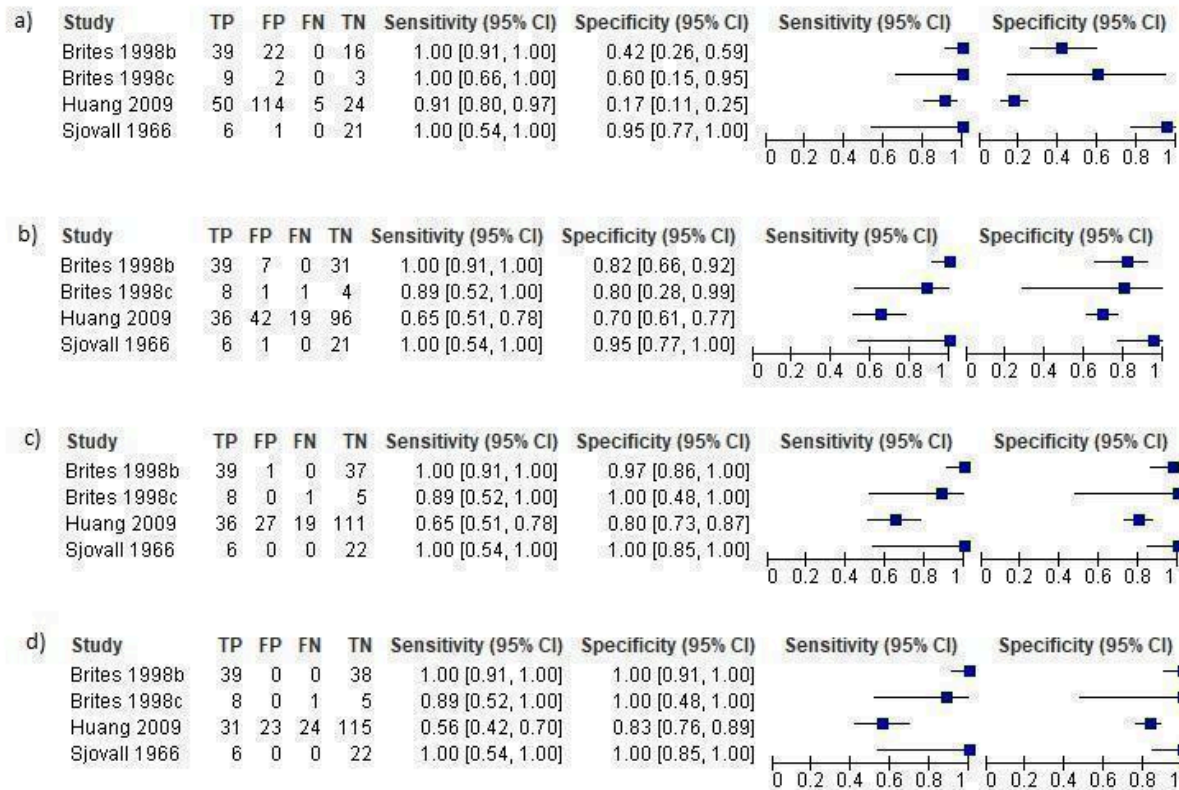
Two studies took into account only the conjugated (tauro- and glyco-) forms of CA, excluding free CA serum levels, because the laboratory techniques used cannot detect the free form as the concentration is too low (Sjovall 1966; Huang 2009). The other two studies for which we had individual participant data also measured free CA levels as separate assessments, but in order to make the study comparable to others we decided not to add them to the CA values (which then comprised only conjugated CA) (Brites 1998b; Brites 1998c).

Chenodeoxycholic acid (CDCA)

We estimated CDCA sensitivity and specificity at two different cut-offs for each study (Figure 13). It was possible to do this because of the availability of individual participant data for all four studies. At a cut-off of 2 µmol/l, the estimated overall sensitivity was 0.98 (95% CI 0.62 to 1.00) and the overall specificity was 0.66 (95% CI 0.19 to 0.94); at a cut-off of 3 µmol/L we could not estimate the overall diagnostic accuracy. High heterogeneity among study results made it impossible to determine the precision of these estimates and their applicability in a real clinical setting.

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Figure 13. Forest plots of chenodeoxycholic acid (CDCA) at different cut-offs for the diagnosis of intrahepatic cholestasis of pregnancy: a) cut-off = 2 µmol/L; b) cut-off = 3 µmol/L
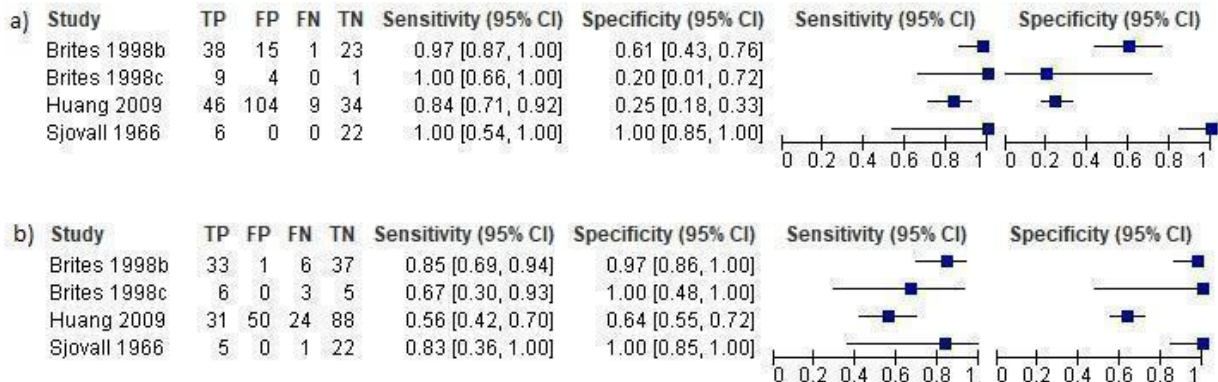
Two studies took into account only the conjugated (tauro- and glyco-) forms of CDCA, excluding free CDCA serum levels, because of the laboratory techniques used which cannot detect the free form as the concentration is too low (Sjovall 1966; Huang 2009). The other two studies for which we had individual participant data measured also free CDCA levels as separate assessments, but in order to make the study comparable to others we decided not to add them to CDCA values provided (which then comprised only conjugated CA) (Brites 1998b; Brites 1998c).

CA/CDCA

No study other than Huang 2009 provided a cut-off for CA/CDCA. We found that for most of the studies, the cut-off corresponding to the Youden index maximum was around 1.8. For this reason, we performed the meta-analysis considering only the cut-off of 1.8. The overall sensitivity was 0.89 (95% CI 0.54 to 0.98), and the overall specificity was 0.92 (95% CI 0.85 to 0.96) (Figure 14).

Figure 14. Forest plot of CA/CDCA with cut-off = 1.8
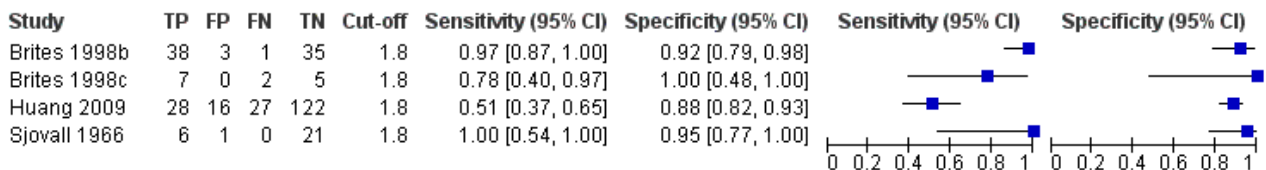
Comparisons

We made indirect comparisons between TSBA for a cut-off of 10 µmol/L and the following index tests for their most accurate cut-off: CA with a cut-off of 3 µmol/L, GCA with a cut-off of 1.5 µmol/L, CA/CDCA with a cut-off of 1.8 µmol/L. We made the indirect comparisons by adding the index tests as covariates to the bivariate or HSROC model. None of the indirect comparisons was found to be statistically significant (TSBA vs CA: P = 0.29; TSBA vs GCA: P = 0.096; TSBA vs CA/CDCA: P = 0.096). An indirect comparison between TSBA for a cut-off of 10 µmol/L and CDCA for a cut-off of 3 µmol/L was not statistically possible.

Direct comparisons were not statistically possible because of the small number of included studies.

Heterogeneity

Taking into account the number and characteristics of the included studies, heterogeneity analysis was possible only for the 11 studies assessing TSBA diagnostic accuracy with cut-off equal to 10 µmol/L. Moreover, this analysis was possible only for some of the sources of heterogeneity planned at the protocol stage: laboratory technique used to measure the index test, therapy (if study patients

underwent therapy with UDCA or not), and timing of measurement of index test (onset of symptoms, peak values among multiple assessments during pregnancy, immediately before delivery). Results are reported below.

Laboratory technique

We investigated laboratory technique by grouping studies according to five different techniques: enzymatic assay (5 studies), enzymatic colorimetric (2 studies), gas-liquid chromatography (1 study), liquid chromatography–mass spectrometry (LC-MS) (1 study), enzymatic fluorometric (2 studies). However, the number of studies for each group was too small to calculate the confidence intervals of accuracy estimates and regions around summary ROC points (except for enzymatic assay). The differences found between techniques were not statistically significant (P = 0.42).

Therapy

We excluded three studies from this heterogeneity analysis because of lack of information regarding therapy (Roger 1994; Huang 2009; Lang 2012); and one because both kind of patients were included (Brites 1998b). We investigated therapy, grouping the seven remaining studies in two different groups: studies including

patients who underwent UDCA therapy (5 studies) and studies including patients who did not (2 studies). The differences found between the two groups in TSBA diagnostic accuracy estimates were not statistically significant (P = 0.60).

Timing

We investigated timing, grouping studies in three groups (onset, peak, delivery) according to when the TSBA measurement took place. Sensitivity and specificity estimated for each group were the following: 0.87 (95% CI 0.68 to 0.96) and specificity 0.87 (95% CI 0.76 to 0.94) for onset; 0.70 (95% CI 0.24 to 0.94) and 1.00 (CI not calculable) for peak; 1.00 (95% CI 1.00 to 1.00) and 0.87 (95% CI 0.68 to 0.95) for delivery. The differences in diagnostic accuracy estimates were statistically significant (P = 0.027).

Sensitivity analysis

At the protocol stage, we had planned to perform a sensitivity analysis 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) in order to explore the influence of the quality of the included studies. However, the overall low quality of included studies did not allow this, as we judged only one study at low risk of bias in all domains (Huang 2009). Hence, we performed only the remaining two sensitivity analyses planned in the protocol.

The first sensitivity analysis excluded studies in which TSBA were included in the reference standard for intrahepatic cholestasis of pregnancy, assuming that this could have been one of the most important sources of bias. The overall sensitivity and specificity were 0.57 (95% CI 0.49 to 0.65) and 0.98 (95% CI 0.53 to 1.00), respectively (Figure 15).

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Figure 15.   Summary ROC Plot of sensitivity analysis of TSBA cut-off=10 µmol/L excluding studies in which TSBA assessment was part of the reference standard. Statistical method used: HSROC (hierarchical summary ROC) model.
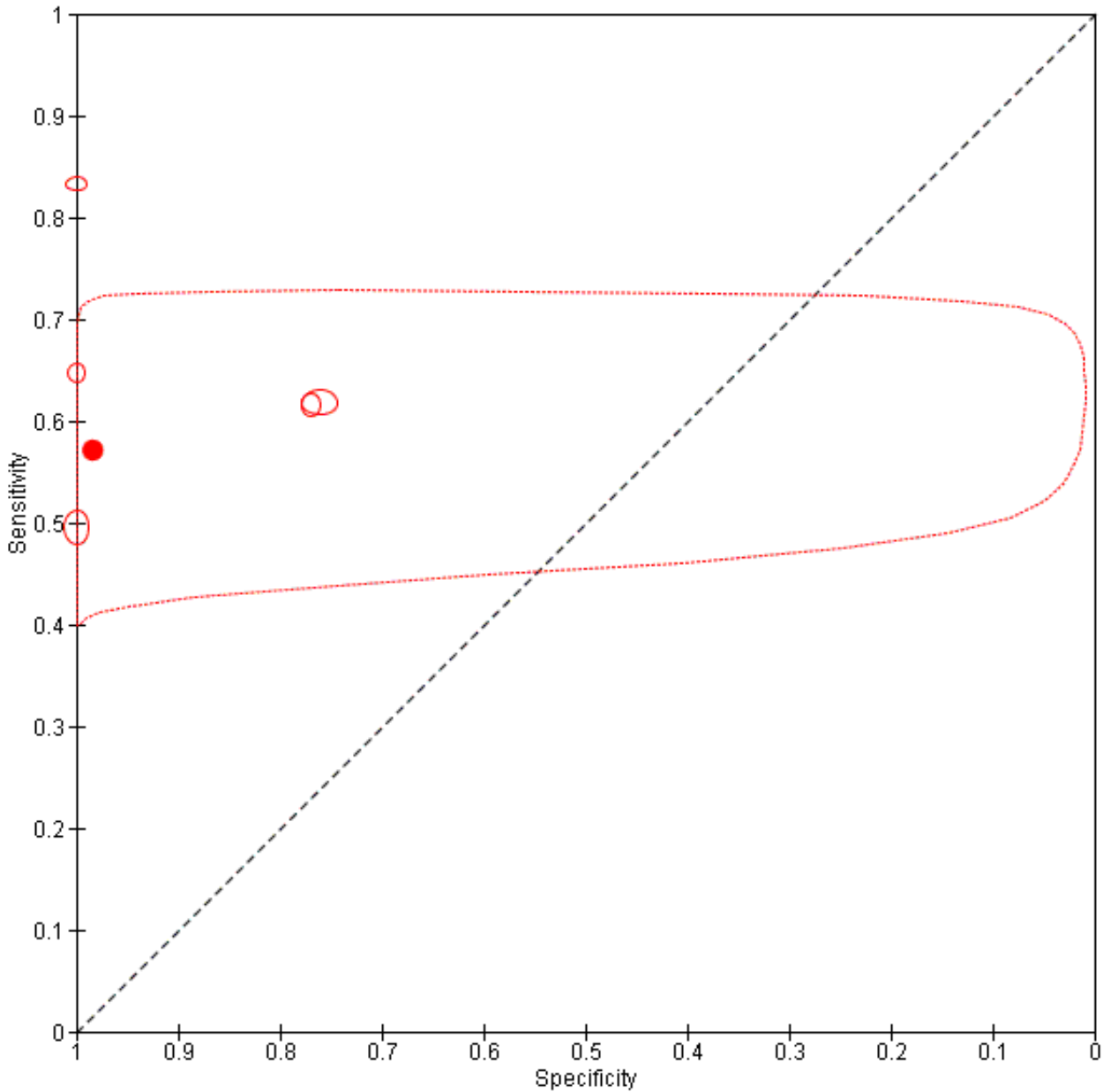
The second sensitivity analysis excluded all studies with case-control design, as all of them enrolled as controls asymptomatic pregnant women. The resultant overall sensitivity and specificity were 0.57 (95% CI 0.48 to 0.66) and 0.92 (95% CI 0.52 to 0.99), respectively (Figure 16).

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Figure 16.   Summary ROC Plot of sensitivity analysis of TSBA cut-off=10 µmol/L excluding studies with case-control design (95% confidence region not estimable because of too few studies included in the analysis). Statistical method used: HSROC (hierarchical summary ROC) model.
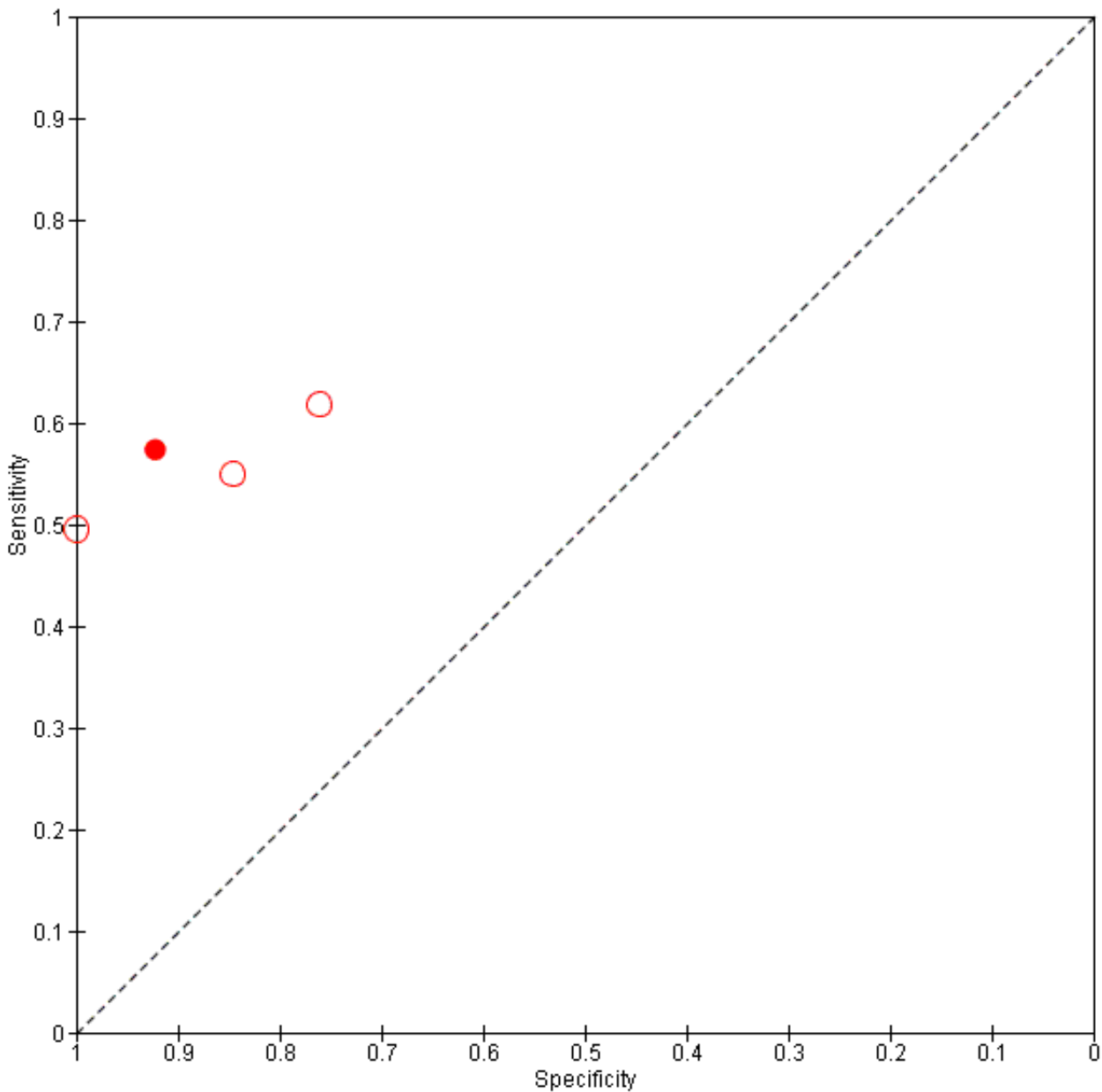
'Summary of findings' table

Summary of findings 1 shows, whenever possible, all considered index tests summary accuracy estimates and consequences of their application in a hypothetical clinical context. In the Summary of findings 1, we give the prevalence of intrahepatic cholestasis of pregnancy of 30% among pregnant women claiming pruritus; that is, the median of prevalences provided by four included studies with a cross-sectional design: Huang 2009 (55/193, prevalence 28%), Lang 2012 (40/66, prevalence 60%), Lunzer 1986 (15/69, prevalence 22%), Roger 1994 (17/49, prevalence 35%). Based on this, we calculated implications of the use of our index tests for the diagnosis of intrahepatic cholestasis of pregnancy on a

hypothetical population of 100 pregnant women with pruritus. For some index tests, especially for GCA and CA, we found a small number of studies, and there was a great heterogeneity in accuracy estimates among them. Hence, we found that the overall accuracy was imprecise, and the confidence intervals (CI) for sensitivity and specificity estimates were very wide or impossible to calculate. To apply these results in a real clinical setting is not possible.

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DISCUSSION

Summary of main results

Our analysis of the eleven studies assessing TSBA diagnostic accuracy for a cut-off of 10 µmol/L (the most used cut-off among the studies we included) provided estimates of sensitivity ranging from 0.72 to 0.98, and specificity ranged from 0.81 to 0.97. Considering the respective pooled estimates of 0.91 and 0.93, in a population of 1000 pregnant women claiming for pruritus, with a prevalence of intrahepatic cholestasis of 30%, 27 (6 to 84) diseased women would be missed, and 49 women (21 to 133) without the disease would be falsely diagnosed. However, with a first sensitivity analysis excluding case-control studies, TSBA overall sensitivity was lower, ranging from 0.48 to 0.66, and its overall specificity had a wider confidence interval, 0.52 to 0.99. This could mean that when patients were pre-selected with a clear diagnosis of intrahepatic cholestasis of pregnancy and compared with healthy and asymptomatic pregnant women, as in most included studies, accuracy of TSBA was higher than when TSBA were performed on a population of symptomatic pregnant women in a real clinical setting. A second sensitivity analysis, with exclusion of studies which comprised TSBA in the reference standard, estimated a sensitivity range from 0.49 to 0.65 and specificity from 0.53 to 1.00. These results support the conclusion that TSBA accuracy may not be so high as believed, and that existent studies about diagnostic accuracy of TSBA are not well designed to assess it. What should have been done before introducing TSBA in clinical practice (and to know better the diagnostic accuracy of TSBA) was the completion of cross-sectional studies enrolling consecutive pregnant women suspected of intrahepatic cholestasis of pregnancy (and followed up after delivery to confirm the right diagnosis). This would have allowed the index test to identify the disease among suspected population (Colli 2014). Only few of the studies included in this systematic review had a design similar to this (Gonzalez 1989; Huang 2009; Lang 2012).

Subgroup analysis considering possible sources of heterogeneity, such as a laboratory technique used to measure TSBA or a therapy for women with intrahepatic cholestasis of pregnancy during pregnancy, did not show statistically significant differences. A heterogeneity analysis considering timing of TSBA testing showed a statistically significant difference: assessing TSBA serum concentration at the time of delivery was more specific but less sensitive in diagnosing intrahepatic cholestasis of pregnancy, while taking the peak value among multiple assessments was more sensitive but less specific than assessing TSBA at the time of onset of symptoms (i.e. pruritus). However, this is not sufficiently clinically relevant, as obstetricians need an index test with high sensitivity at an earlier time, which can allow them to strictly follow up the pregnant woman and her foetus in order to find, as soon as possible, signs of potential fetal distress and to decide the best management. If diagnosis is made at the time of delivery, it is too late and almost useless, because it means that a fetal adverse event (fetal death) did not occur; if we make multiple assessments during pregnancy, the evaluation of the peak value could be only 'a posteriori'.

The data to allow a direct comparison between index tests were limited. Through indirect comparisons, none of the serum bile acid profile components were shown to be better than TSBA. However, there were too few and biased studies included and analysed to obtain a precise estimate of serum bile acid profile accuracy.

We could not analyse the accuracy of combinations of the index tests (that in our review protocol was defined as TSBA plus any component of serum bile acid profile) as none of the included studies did so.

Strengths and weaknesses of the review

To our knowledge, this is the first systematic review on the accuracy of diagnostic tests for intrahepatic cholestasis of pregnancy. The rigorous methodology adopted in all phases of the work is a strength of this review: our findings are based on a thorough searching of studies and strict inclusion criteria, as well as standardised and independent data extraction and analysis. Another strength of our review is our success in contacting many study authors to retrieve individual participant data and useful additional data: this allowed us to make more analyses than would have been possible based only on published data.

Major limitations are: the small number of included studies, especially for serum bile acid profile components; the overall low quality of included studies due to a design that was not properly tailored for diagnostic accuracy, and inclusion of the index tests in the reference standard; the relatively small sample sizes of study participants; and the unexplained heterogeneity among studies on serum bile acid profile, most probably due to other possible sources of heterogeneity, not planned at the protocol stage.

Applicability of findings to the review question

The overall low quality, high risk of bias, and great heterogeneity of the results of some index tests prevents us from reaching definitive conclusions and making recommendations. Thus, at present, we do not find any compelling evidence to recommend or refute the routine use of any of these tests in clinical practice.

AUTHORS' CONCLUSIONS

Implications for practice

So far, TSBA diagnostic accuracy for intrahepatic cholestasis of pregnancy might have been overestimated: TSBA can add some more information, but they should not be used as the most reliable and unique marker for the diagnosis of intrahepatic cholestasis of pregnancy. Our review suggests to obstetricians who suspect intrahepatic cholestasis of pregnancy in a pregnant woman claiming for pruritus that they may not base their evaluation only on TSBA levels. To consider all possible differential diagnoses with the use of other laboratory and imaging tests, consulting a hepatologist if needed, may be of help.

Implications for research

As evidence on intrahepatic cholestasis of pregnancy is lacking and current clinical practice questionable, we need continuous primary clinical research. New insights into the pathogenesis of intrahepatic cholestasis of pregnancy may help to find out more accurate biomarkers for the disease, both diagnostic and prognostic. We need well-designed diagnostic test accuracy studies with a cross-sectional prospective design on pregnant women suspected for intrahepatic cholestasis of pregnancy (i.e. with onset of pruritus during pregnancy), assessing total serum bile acids (TSBA) or components of serum bile acid profile concentrations, independently or in combination, and comprehensive evaluation of fetal outcomes, with a clear and unbiased definition of the

reference standard for the disease (with an eight weeks' follow-up after delivery assessing normalisation of liver tests). This will allow estimating the diagnostic and prognostic accuracy of these tests with high quality of evidence. Such studies ought to be reported according to the STARD statement.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Almuna 1986

Study characteristics	
Patient sampling	Case-control, prospective, single centre study.
	Time span considered and total number of women screened for inclusion not provided.
	Cases: 55 pregnant women with pruritus (generalised or palm-plantar, mostly at night) in the absence of other dermatological or allergic diseases, were enrolled as patients with ICP.
	Controls: 136 pregnant women without symptoms and without clinical and laboratory evidence of hepato-biliary diseases, who did not take drugs for at least a week before the time of the assessment, were enrolled as controls.
Patient characteristics and setting	Setting: Hospital Militar de Santiago, Chile
	Characteristics of patients in case group: gestational age 28 to 39 weeks. Age of patients not provided.
	Characteristics of patients in control group: age 20 to 38 years old, gestational age 29 to 41 weeks
Index tests	Glycocholic acid, performed on serum samples of pregnant women at fasting (all participants) or postprandial (in all 55 patients and only 25 controls) status. Patients were tested when the suspicion of disease arose following pruritus.
	Laboratory technique: enzyme immunoassay ("ENDAB Cholyglicine, Enzime Immunoassay")
	Diagnostic cut-off values: > 0.7 µg/L. Defined only after controls test results were found (their highest value was 0.66 µg/L).
Target condition and reference standard(s)	ICP and clinical diagnosis including follow-up assessing spontaneous relief of pruritus after delivery, assessed by obstetricians. They were blind to the index test results.
Flow and timing	Glycocholic acid was performed at a fasting status in all participants after week 29 of pregnancy, and all of them were included in the analysis. At a postprandial status, it was performed in all 55 patients and only in 25/136 controls, and all of them were included in the analysis. All patients were followed-up after delivery.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	No		

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Almuna 1986 *(Continued)*

Did the study avoid inappropriate exclusions?	Yes			
		High		**Low**

DOMAIN 2: Index Test Component(s) of serum bile acid profile

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes			
If a threshold was used, was it prespecified?	No			
		High		**Low**

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Unclear			
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes			
Was the index test not part of the reference standard?	Yes			
		Unclear		**Low**

DOMAIN 4: Flow and Timing

Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
	Low	

Almuna 1987b

Study characteristics

Patient sampling	Case-control, prospective, single centre study
	Time span considered and total number of women screened for inclusion not provided.
	Cases: 22 pregnant women who underwent cesarean section after week 36 of pregnancy were enrolled at the time of delivery.
	8 women were enrolled as patients with clinical diagnosis of ICP. They had pruritus, at least 3 previous determinations of fasting glycocholic acid > 0.7 µg/L, and absence of other possible maternal or fetal diseases.

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Almuna 1987b *(Continued)*

	Controls: 14 women were enrolled, after exclusion of personal history of liver diseases, anaemia, diabetes, hypertension, urinary infections, Rh sensibilization, post-term pregnancy, fetal distress or malformations.
Patient characteristics and setting	Setting: Military Hospital de Santiago, Chile Pregnant women enrolled at the time of cesarean delivery. They were pre-selected with at least 3 previous determinations of fasting glycocholic acid > 0.7 µg/L
Index tests	Glycocholic acid (GCA) tested on serum fasting samples collected from pregnant women at the time of cesarean section (see notes) Laboratory technique: enzyme immunoassay ("ENDAB Cholyglicine, Enzime Immunoassay") Predefined cut-off value: 0.7 µg/L Individual participant data regarding glycocholic acid assessment are given in the publication.
Target condition and reference standard(s)	ICP and clinical diagnosis including follow-up after delivery assessing disappearance of pruritus. The index test was part of the reference standard, obstetricians who assessed the reference standard were not blind.
Flow and timing	Glycocholic acid performed at the time of cesarean section in all patients. Follow-up after delivery assessing disappearance of pruritus in all patients
Comparative	
Notes	The study analysed glycocholic acid concentration in maternal serum, cord blood and amniotic fluid tested on samples collected at the time of cesarean section. We considered for our analysis only maternal serum samples, according to our review question.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	No		
		High	High
DOMAIN 2: Index Test Component(s) of serum bile acid profile			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low

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Almuna 1987b *(Continued)*

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	No
Was the index test not part of the reference standard?	No

	High	Low

DOMAIN 4: Flow and Timing

Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes

Low

Brites 1998b

Study characteristics

Patient sampling	Case-control, prospective, single centre study
	39 pregnant women were enrolled as patients with ICP from the largest maternity ward and hospital in Lisbon (Portugal). They had:
	- severe pruritus
	- total serum bile acids > 10 µmol/l, with cholic acid representing > 40%
	- at least one elevated among aminotransferases or bilirubin
	- absence of any other known disease that could cause liver dysfunction (chronic liver disease, symptomatic cholelithiasis, viral hepatitis).
	The total number of woman screened for inclusion was not recorded. The prevalence of the disease at the time of the study was about 1.5%.
	38 pregnant women were enrolled from "routine antenatal clinics" as controls.
	20 healthy non-pregnant women were also studied, but we didn't include them in our analysis following our inclusion criteria.
	Important data which could not be found in the publication were received by email from authors (see notes).
Patient characteristics and setting	Characteristics of patients in case group: 19 to 41 years old, at their 33.4 ± 4.4 week of pregnancy. They were pre-selected for having total serum bile acids > 10 µmol/l, of which cholic acid representing > 40%.

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Brites 1998b *(Continued)*

	Characteristics of patients in control group: 18 to 44 years old, at their 30.0 ± 6.6 week of pregnancy.

| Index tests | Total serum bile acids (TSBA), cholic acid (CA), glycocholic acid (GCA), chenodeoxycholic acid (CDCA), de-oxycholic acid (DCA), lithocholic acid (LCA), total glyco-conjugated acids (G-c), total tauro-conjugated acids (T-c), CA/CDCA, G-c/T-c, evaluated on serum fasting samples taken at the time of diagnosis (see notes)

Laboratory techniques used:

- for total serum bile acids: enzymatic-fluorometric assay
- for conjugated serum bile acids: high-pressure liquid chromatography (HPLC)
- for unconjugated serum bile acids: enzymatic-fluorometric method following thin-layer chromatography using silica gel plates

NB: in the study, "unconjugated ursodeoxycholic acid was not individually quantified because it does not separate from chenodeoxycholic acid during thin-layer chromatography".

Cut-off value for total serum bile acids: > 10 µmol/l, predefined.

Cut-off values (in µmol/l) for other index tests: GCA > 2, CA/CDCA > 1.5, G-c/T-c < 1.0. All defined only after data analysis. |
|---|---|
| Target condition and reference standard(s) | ICP and clinical diagnosis including the follow-up after delivery showing disappearance of pruritus and nor-malisation of bile acids and previously found abnormal liver tests within 1 month. |
| Flow and timing | Index tests performed in all participants (in patients, at the time of diagnosis). All patients were followed up after delivery for 1 month. |
| Comparative | |
| Notes | Following e-mail correspondences with Dora Brites (see study references), we received detailed inclusion criteria and individual participant data, regarding laboratory findings needed for our analysis.

In particular, individual data received were: serum concentrations of total bile acids (TSBA), glyco/tau-ro/free cholic acid (GCA,TCA, fCA), glyco/tauro/free chenodeoxycholic acid (GCDCA, TCDCA, fCDCA), gly-co/tauro/free deoxycholic acid (GDCA, TDCA, fDCA), glyco/tauro ursodeoxycholic (GUDCA, TUDCA) and gly-co/tauro/free lithocholic acid (GLCA, TLCA, fLCA).

Using received data, we calculated:

- CA as the sum of GCA and TCA
- CDCA as the sum of GCDCA and TCDCA
- CA/CDCA ratios were obtained from data calculated above

We did not consider the free forms of CA and UDCA in the sums described above, in order to allow a com-parison of the value of CA and CDCA provided by these studies with values provided in the other studies assessing their diagnostic accuracy; in fact, owing to the techniques used, they measured only the sum of conjugated forms of CA and CDCA, without their free form. |

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of pa-tients enrolled?	No		
Was a case-control de-sign avoided?	No		

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Brites 1998b *(Continued)*

Did the study avoid inappropriate exclusions?	No		
		High	**High**

DOMAIN 2: Index Test Total serum bile acids

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**

DOMAIN 2: Index Test Component(s) of serum bile acid profile

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
		High	**Low**

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
Was the index test not part of the reference standard?	No		
		High	**Low**

DOMAIN 4: Flow and Timing

Did all patients receive the same reference standard?	Yes		

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Brites 1998b *(Continued)*

Were all patients included in the analysis?	Yes

<div align="center">

Low

</div>

Brites 1998c

Study characteristics	
Patient sampling	case-control, prospective, multicentre study
	Pregnant women attending two centres from 1994 to 1997 were considered for inclusion (total number screened not provided).
	Cases: 16 women with ICP were enrolled as patients. They had:
	• severe pruritus • total serum bile acids > 10 μmol/l, with cholic acid representing > 40% • at least 1 elevated of aminotransferases or bilirubin • absence of any other known disease that could cause liver malfunction
	Of these patients, 7 patients were treated with UDCA therapy (14 mg/Kg/day, from 21 days before the term to the time of delivery), while 9 patient were not treated.
	We received additional information from authors (see notes).
	Controls: 5 healthy pregnant women at full-term gestation, without history of hepatic disease or preeclampsia, were voluntary enrolled as controls.
Patient characteristics and setting	Setting: Santa Maria Hospital, Garcia de Orta Hospital and Dr. Alfredo da Costa Maternity Ward (Portugal)
	Characteristics of patients in case group: 16 to 35 years old, 28 to 37 week of pregnancy at the time of diagnosis. They were
	pre-selected for having total serum bile acids > 10 μmol/L, with cholic acid representing > 40%.
Index tests	Total serum bile acids and cholic acid (CA), glycocholic acid (GCA), chenodeoxycholic acid (CDCA), deoxycholic acid (DCA), lithocholic acid (LCA), total glyco-conjugated (G-c) and total tauro-conjugated (T-c) acids, CA/CDCA, G-c/T-c (see notes)
	The index tests were assessed on serum fasting samples taken at the time of delivery.
	Laboratory techniques:
	• for total serum bile acids: enzymatic-fluorometric assay (following solid-phase extraction) • for conjugated serum bile acids: high-pressure liquid chromatography (HPLC) • for unconjugated serum bile acids:enzymatic-fluorometric method (following solid-phase extraction and thin-layer chromatography using silica gel plates)
	NB: in the study, "unconjugated ursodeoxycholic acid was not individually quantified due to difficult separation from chenodeoxycholic acid during thin-layer chromatography".
	Diagnostic cut-off value for TSBA: 10 μmol/l
	Cut-off values not provided for any of the other index tests
	For total serum bile acid analysis, we included in our analysis all 21 selected participants.

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

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Brites 1998c *(Continued)*

	For serum bile acid profile components analysis, we obtained individual data (received from authors, see notes) for only the 9 non-treated patients and the 5 controls.
Target condition and reference standard(s)	ICP and clinical evaluation including follow-up after delivery (see notes)
Flow and timing	Index tests and reference standard performed in all participants at the time of delivery
	Follow-up after delivery not performed in all patients (see notes)
Comparative	
Notes	The primary aim of the study was to investigate bile acid concentration in colostrum of women with ICP, and to compare them with serum concentrations. We considered only data regarding concentration of the index tests performed on maternal serum.
	Following e-mail correspondences with Dora Brites (see study references), we received:
	1. detailed inclusion criteria for participants
	2. individual data of the 9 non-treated patients and 5 controls
	Among the individual data we received, were: serum concentrations of total bile acids (TSBA), glyco/tauro/free cholic acid (GCA,TCA, fCA), glyco/tauro/free chenodeoxycholic acid (GCDCA, TCDCA, fCDCA), glyco/tauro/free deoxycholic acid (GDCA, TDCA, fDCA), glyco/tauro ursodeoxycholic (GUDCA, TUDCA) and glyco/tauro/free lithocholic acid (GLCA, TLCA, fLCA).
	Using received data, we calculated:
	• CA as the sum of GCA and TCA
	• CDCA as the sum of GCDCA and TCDCA
	• CA/CDCA ratios were obtained from data calculated above.
	We did not consider the free forms of CA and UDCA in the sums described above, in order to allow a comparison of the value of CA and CDCA provided by these studies with values provided in the other studies assessing their diagnostic accuracy: in fact, owing to the techniques used, they measured only the sum of conjugated forms of CA and CDCA, without their free form.
	3. Information on follow-up after delivery to assess the spontaneous relief of symptoms and normalization of liver tests: "some patients did not return to the hospital to see whether they have returned to normal. However, the majority were evaluated as accomplishing this item".

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	No		

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Brites 1998c *(Continued)*

	High	High

DOMAIN 2: Index Test Total serum bile acids

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	

	Low	Low

DOMAIN 2: Index Test Component(s) of serum bile acid profile

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	No	

	High	Low

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	No	
Was the index test not part of the reference standard?	No	

	High	Low

DOMAIN 4: Flow and Timing

Did all patients receive the same reference standard?	No	

Brites 1998c *(Continued)*

Were all patients included in the analysis?	No

High

Gonzalez 1989

Study characteristics	
Patient sampling	Cross-sectional, prospective, single centre study
	All 10,711 pregnant women admitted to the centre during a 12-month period between the years 1983 and 1984, were serially evaluated and followed up during their pregnancy for the diagnosis of ICP.
	Among the women with twin pregnancies, only the 62 who underwent complete physical examination and clinical and laboratory follow-up until one week post-partum were consecutively enrolled in the study (see notes).
	The prevalence of the disease obtained in the study was about 20.9% among twin pregnancies and 4.7% among singleton pregnancies.
Patient characteristics and setting	Setting: Hospital del Salvador (Chile)
	Characteristics of patients: 66 had twin pregnancy, and 10,645 had singleton pregnancy.
	Singleton pregnancies were excluded.
Index tests	Total serum bile acids. The test was serially performed during a follow-up of each pregnant woman until 1 week post-partum. The values provided in the publication are the highest found during pregnancy (peak values).
	Laboratory technique: enzymatic method of Mashige et al (Mashige 1976)
	Predefined diagnostic cut-off value: 10 µmol/L
Target condition and reference standard(s)	ICP and clinical diagnosis based on widespread skin pruritus, appearing in the second half of pregnancy and lasting until delivery, with total serum bile acids above 10 µmol/L, exclusion of other cholestatic diseases, follow-up after delivery assessing spontaneous relief of symptoms and normalisation of previously found abnormal liver function tests. Reference standard assessed by obstetricians, who were not blind for the index test.
Flow and timing	Every participant was serially evaluated and followed up during pregnancy, with complete physical examination and clinical and laboratory tests until 1 week after delivery. The values provided for the index test are the peak values found during pregnancy.
Comparative	
Notes	The study included all twin pregnancies recruited consecutively during a 1-year period. Among the 10,645 singleton pregnancies admitted in the same period at the hospital, 492 were diagnosed with ICP, but authors included only 14 of them in their analysis, without explaining the criteria used to select them. We decide to exclude them from our analysis as their enrolment was not comparable to that used for twins.
	We do not know if the exclusion of singleton pregnancies and an analysis based only on twins may affect the applicability of the findings to clinical practice.

Methodological quality	

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Gonzalez 1989 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Unclear**
DOMAIN 2: Index Test Total serum bile acids			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
Was the index test not part of the reference standard?	Yes		
		High	**Low**
DOMAIN 4: Flow and Timing			
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

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Guducu 2013

Study characteristics

Patient sampling	Case-control, retrospective, single centre study
	Data of women who delivered at the centre between January 2008 and May 2013 were screened for inclusion (total number not provided).
	Cases: 20 women were enrolled as patients with ICP, for having pruritus with elevated total serum bile acids (> 10 μmol/L) or elevated liver aminotransferases, or both, in the absence of other possible liver diseases.
	Controls: 21 healthy pregnant women without pruritus were enrolled as controls.
	Exclusion criteria for participants were: diabetes mellitus, hypertensive diseases of pregnancy, diseases of thyroid gland, haematological abnormalities, use of drugs other than multivitamins or iron.
Patient characteristics and setting	Setting: Istanbul Bilim University Avrupa Florence Nightingale Hospital (Turkey)
	Characteristics of patients in case group: pre-selected for having total serum bile acids > 10 μmol/L
	Women with diabetes mellitus, hypertensive diseases of pregnancy, diseases of thyroid gland, haematological abnormalities, use of drugs other than multivitamins of iron were excluded from the study.
	All participants were between 24 and 38 years old and after their 25th week of pregnancy.
Index tests	Total serum bile acids. Assessed on serum fasting samples. In patients, serum sample was taken at the time of onset of symptoms.
	Predefined diagnostic cut-off value: 10 μmol/L (see notes)
	Laboratory technique: enzymatic assay (see notes)
Target condition and reference standard(s)	ICP and clinical evaluation including follow-up after delivery assessing relief of symptoms and normalisation of liver tests in all patients.
Flow and timing	Index test performed after onset of pruritus (after week 25 of pregnancy). Follow-up after delivery assessing relief of symptoms and normalisation of liver tests in all patients.
	Exclusion of 6 patients and 2 controls for lacking data on total serum bile acids, thus leading to a final inclusion in the analysis only 14 patients and 19 controls.
Comparative	
Notes	Following e-mail correspondences with Nilgun Kutay Guducu (see references), we received the information listed below.
	• Individual participants' data
	• Diagnostic cut-off value for total serum bile acids: 10 μmol/L
	• Laboratory technique: enzymatic assay
	• Serum samples taken in fasting status
	• The follow-up after delivery assessing spontaneous relief of symptoms and normalisation of liver biochemistry was performed in all patients.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			

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Guducu 2013 *(Continued)*

Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	No		
		High	High

DOMAIN 2: Index Test Total serum bile acids

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
Was the index test not part of the reference standard?	No		
		Low	Low

DOMAIN 4: Flow and Timing

Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		High	

Huang 2009

Study characteristics

Patient sampling	Cross-sectional, retrospective multicentric study

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Huang 2009 *(Continued)*

	All serum samples with complete bile acids and transaminases analysis from pregnant women attending clinics and hospitals of a corporation and sent to a unique laboratory between 1 January 2006 and 31 December 2006 were retrospectively considered. Authors assumed that bile acid testing was requested because of suspicion of ICP. Of 262 specimens, only 231 specimens from 208 pregnant women had complete data regarding bile acids and transaminases and were included (see notes). Having received individual participant data from authors, we decided to include only 1 specimen for each of the 208 women considered: in particular, whithin the database given by authors, we considered the first written specimen for each ID with multiple determinations, assuming that it was the first one collected as soon as the suspicion of diseases arose (see notes). Hence, the number of specimens finally included was 193.
Patient characteristics and setting	Setting: clinics and hospitals of Health and Hospital Corporation (New York). Serum samples sent to Quest Diagnostic Nichols Institute, San Juan Capistrano, CA, USA Serum samples were included if complete bile acids and transaminase data were available, assuming that they were performed because of the suspicion of ICP. In our opinion, the retrospective study design starting from laboratory test requests on serum samples, instead of starting from clinical suspicion of disease, does not allow a clear evaluation of the applicability of participant selection.
Index tests	**Total serum bile acids, CA/CDCA (published data)**. CA, CDCA, DCA (unpublished data, see notes) Diagnostic cut-off values provided in the publication ("supplied by the laboratory"): TSBA > 19.2 μmol/l, CA/CDCA > 3.4. Serum samples were analysed at Quest Diagnostic Nichols institute, San Juan Capistrano, CA, USA. Through the web site of the laboratory (www.questdiagnostics.com/testcenter/BUOrderInfo.action?tc=8482N&labCode=SJC) we found: • laboratory technique used: Liquid Chromatography Tandem Mass Spectrometry (LC/MS/MS) • diagnostic cut-off values for: CA > 3.1, CDCA > 9.9, DA > 7.3
Target condition and reference standard(s)	ICP and clinical evaluation including a "general evaluation for resolution of symptoms at the post-partum visit" (see notes)
Flow and timing	It is assumed that index tests were performed when the suspicion of ICP came out, but not provided any specific time point. A "general evaluation for resolution of symptoms at the post-partum visit" took place (see notes).
Comparative	
Notes	Following email correspondences with William Huang (see study references), we received the following information. • A follow-up after delivery took place ("The patients were generally evaluated for resolution of symptoms at the postpartum visits") • Individual participant data On the basis of individual participant data, we decided to redefine the index tests cut-off values and the reference standard. The reference standard for the target condition as defined by authors was any elevation of total serum bile acids (> 19.2 μmol/L), or CA/CDCA (> 3.4) or liver biochemistry tests (ASP > 39 U/L, ALT > 35 U/L), assuming that they were performed in the suspicion of disease. This do not match with our review question. So, having received individual participant data from authors, we decided to redefine the reference standard as any elevation of serum aminotransferases (ASP>39 or ALT>35, or both) and clinical evaluation including "resolution of symptoms at the postpartum visit" (that took place for all patients, as supplied by authors), assuming (as authors did) that participants who underwent bile acid testing had suspicious symptoms for intrahepatic cholestasis.

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Huang 2009 *(Continued)*

Moreover, we redefined the diagnostic cut-off values as follows.

- TSBA > 10 µmol/L
- CA multiple cut-offs
- CDCA multiple cut offs
- CA/CDCA > 1.8

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Unclear
DOMAIN 2: Index Test Total serum bile acids			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 2: Index Test Component(s) of serum bile acid profile			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correct-	Yes		

Huang 2009 *(Continued)*
ly classify the target
condition?

Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Was the index test not part of the reference standard?	Yes		
		Low	**Unclear**

DOMAIN 4: Flow and Timing

Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
		Low

Jiang 2012

Study characteristics

Patient sampling	Case-control, retrospective, single centre study
	Among 4930 total deliveries taking place at 1 hospital between January 2010 and August 2011, 350 pregnant women with ICP (incidence 7.1%) were enrolled as cases, and 350 pregnant women with uncomplicated pregnancies were enrolled as controls.
	Inclusion criteria for pregnant women diagnosed with ICP were:
	• pruritus or icterus during pregnancy, or both
	• total serum bile acid above 10 µmol/L, or serum glycocholic acid above 10.75 µmol/L, or mild to moderate rise of liver biochemistry tests
	• exclusion of other possible dermatological or liver diseases responsible for pruritus
Patient characteristics and setting	Setting: First Affiliated Hospital, Chongqing (China)
	Characteristics of patients in case group: 18 to 45 years old
	Characteristics of patients in control group: 19 to 42 years old
Index tests	Total serum bile acid. Not mentioned if serum samples were taken at fasting or post-prandial status of pregnant women.
	Laboratory technique: automatic biochemical Analyzer (7170A) which uses an enzymatic method.
	Diagnostic cut-off value: not predefined, but derived from ROC curves as > 11 µmol/L.
	Provided sensitivity: 70.6%

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Jiang 2012 *(Continued)*

	Provided specificity: 88.0%
Target condition and reference standard(s)	ICP and clinical evaluation comprising follow-up after delivery assessing spontaneous relief of symptoms and normalisation of liver tests. Reference standard assessed by obstetricians, who were not blind for the index test as it was part of their evaluation.
Flow and timing	All patients were assessed with total bile acids at the time of onset of symptoms and were followed up after delivery to assess spontaneous relief of symptoms and signs.
Comparative	
Notes	The translation of the article and the extraction of data was possible thanks to Ms Maoling Wei.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	No		
		High	Low
DOMAIN 2: Index Test Total serum bile acids			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
		High	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
Was the index test not part of the reference standard?	No		
		High	Low
DOMAIN 4: Flow and Timing			

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Jiang 2012 *(Continued)*

Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes

Low

Kowalska-Kanka 2013

Study characteristics	
Patient sampling	case-control, retrospective, single centre study
	Among all pregnant women (total number not provided) attending 1 institute between March 2009 and September 2011, 33 were enrolled as patients for having pruritus, elevated aminotransferases, total total serum bile acids > 11 µmol/L, absence of other liver diseases.
	40 women with uncomplicated pregnancy and fetal well-being were selected as controls.
	The ethnicity of all women was Caucasian.
	Exclusion criteria for all participants were anaemia, kidney disease, bone diseases, acute or chronic bleedings in pregnancy, and pre-eclampsia.
Patient characteristics and setting	Setting: Institute of Mother and Child, Warsaw (Poland)
	Characteristics of patients in case group: 21 to 42 years old, 8 twin pregnancies and 25 singleton; pre-selected for having total serum bile acids > 11 µmol/L.
	Characteristics of patients in control group: 20 to 40 years old, 6 twin pregnancies and 34 singleton
	Exclusion criteria for all participants were anaemia, kidney disease, bone diseases, acute or chronic bleedings in pregnancy, and pre-eclampsia (see notes).
Index tests	Total serum bile acids. Samples taken at a fasting status. Value provided for TSBA are peak values found among multiple assessments during pregnancy.
	Laboratory technique: enzymatic colorimetric assay (Randox bile acids kit and reagent)
	Predefined cut-off value: 11 µmol/L
Target condition and reference standard(s)	ICP and clinical evaluation including an assessment with "laboratory tests of hepatic parameters (AST, ALT, bilirubin)" that "were performed two weeks after delivery" (information received by authors, see notes). Reference standard performed by the obstetrician, who was not blind for the index test as it was part of his evaluation.
Flow and timing	TSBA values provided are peak values among multiple assessments during pregnancy, found at week 30 to 38 of pregnancy in patients and at week 31 to 40 in controls (see notes). Assessment of liver tests' normalisation performed 2 weeks after delivery in all patients (see notes).
Comparative	
Notes	The aim of the study was to assess the correlation between bile acids and erythropoietin in pregnant women with ICP. Thus, selected participant may not match properly our review question.
	Following email correspondences with Aneta Kowalska-Kanka (see study references), we received the information listed below.

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

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Kowalska-Kanka 2013 *(Continued)*

- Value provided for TSBA are peak values found among multiple assessments during pregnancy, at week 30 to 38 of pregnancy in patients and at week 31 to 40 in controls
- Serum samples were taken at a fasting status
- Laboratory tests of hepatic parameters (AST, ALT, bilirubin) were performed two weeks after delivery, to assess their normalisation
- In the patients group there were 5 women without pruritus at the time of bile acid assessment. This was because "pruritus was the first sign of ICP in the all cases. It was the reason to check TBA and other laboratory tests. Pregnant women with ICP were hospitalised and treated with UDCA for few weeks, until delivery time. During this time TBA concentration changed, same as pruritus intensity. We checked it once a week and we observed (in few cases) elevated TBA without pruritus. I had to choose only one result of TBA concentration".
- Individual participant data

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	No		
		High	High
DOMAIN 2: Index Test Total serum bile acids			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		

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

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Kowalska-Kanka 2013 *(Continued)*

		High	Low
Was the index test not part of the reference standard?	No		

DOMAIN 4: Flow and Timing			
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

	Low	

Laatikainen 1984

Study characteristics	
Patient sampling	Case-control, retrospective, single centre study
	All 117 pregnant women referred because of pruritus and elevated serum aminotransferases to one hospital during 1980 to 1981 were included as cases (total number screened for inclusion not provided). 60 healthy pregnant women were included as controls.
Patient characteristics and setting	Setting: Helsinki University Central Hospital, Helsinki (Finland)
	Characteristics of patients in case group: mean age 30.2 years
	Characteristics of patients in control group not provided (only said that they were "healthy")
Index tests	Total serum bile acids. The values provided in the publication were performed 1 week before delivery. Not provided if serum samples were taken at a fasting or postprandial status.
	Technique: enzymatic method
	The range of normal values provided by the publication for controls is 0 to 5 µmol/L, but it is not clear if a concentration above 5 µmol/l was considered diagnostic. Thus, as data concerning this cut-off value were insufficient to complete a two-by-two table, we redefined a diagnostic cut-off value of 10 µmol/L (see notes).
Target condition and reference standard(s)	ICP and clinical evaluation including follow-up after delivery assessing normalization of symptoms and laboratory tests. The reference standard was assessed by obstetricians, who were not blind for the index test.
Flow and timing	Total serum bile acid values provided in the publication were collected 1 week before delivery in all pregnant women diagnosed with ICP. A follow-up after delivery assessing normalization of symptoms and laboratory tests was performed in all patients.
Comparative	
Notes	The diagnostic cut-off value for total serum bile acids provided in the publication is not clear, as authors only stated that the normal range found in the control group was between 0 and 5 µmol/L. For case group, it is provided only a table with the description of the 3 subgroups in which women were divided. The 3 subgroups were defined on total serum bile acids concentrations: group A (TSBA < 10

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µmol/L), with 59 women; group B (TSBA from 10 to 40 µmol/L), with 37 women; group C (TSBA > 40 µmol/L) with 21 women. It is not clear if group A had a serum bile acid level between 5 and 10 or between 0 and 10 µmol/L. We therefore decided to consider as diagnostic a cut-off value of 10 µmol/L, in order to have complete and unquestionable data to complete a two-by-two table.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	Yes		
		High	Low
DOMAIN 2: Index Test Total serum bile acids			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
Was the index test not part of the reference standard?	Yes		
		High	Low
DOMAIN 4: Flow and Timing			
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Low

Lang 2012

Study characteristics

Patient sampling	Cross-sectional, retrospective, single centre study
	A retrospective audit of bile acids performed in all pregnant women suspected of ICP attending 1 centre between February 2009 and January 2010 was performed.
	118 bile acid requests (associated with ALT) for 70 women were found, and linked to the patients' charts to assess the final diagnosis (see notes). Complete data to allow our analysis were available for 66 women (4 women lacked serum bile acid assessment result, see notes).
Patient characteristics and setting	Setting: Royal Jubilee Maternity Hospital, Belfast (UK)
	The treatments received by women diagnosed with ICP were: 53% vitamin K, 63% UDCA, 33% topical therapy, 65% anti-histamines.
	The ethnicity of participants was mostly 'white', except for 3 women coming from India (1), Pakistan (1) and Nepal (1).
Index tests	Total serum bile acids. Assessed on serum fasting samples taken at the time of diagnosis
	Laboratory technique: Randox Total Bile Acid kit (enzymatic colorimetric method)
	Cut-off value provided in published poster: 14 µmol/l (authors sent us individual patients data and their analysis, providing sensitivity and specificity calculated at each possible cut-off value)
Target condition and reference standard(s)	ICP and RCOG Green-top guideline n.43 diagnostic criteria (Green-top Guideline No.43), assessed by obstetricians, who were not blind for the index test.
Flow and timing	Total bile acids were performed at the time of diagnosis (between week 28 to 40 of pregnancy, except for 2 patients before week 28) or they were assessed multiple times during pregnancy (see notes). The diagnosis was retrospectively confirmed viewing the women's charts and following the RCOG Green-top guideline n.43 criteria (Green-top Guideline No.43). All data from participants meeting the inclusion criteria were analysed.
Comparative	
Notes	• We received further information on the study and individual participant data by email from Tim Lang (see study references).
	• The diagnosis of ICP was finally confirmed in 43 women (40 included in our analysis) and ruled out in 27 women (26 included in our analysis) through a retrospective view of the women's chart, if they fulfilled the diagnostic criteria stated by the Green-top Guideline n.43.
	• Following individual participant data, we could finally include 66 women, as data on total serum bile acid levels for 4 women were lacking.
	• When multiple assessments were performed, we included for our first analysis only the first one (onset of symptoms).

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			

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

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Lang 2012 *(Continued)*

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**

DOMAIN 2: Index Test Total serum bile acids

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
Was the index test not part of the reference standard?	Yes		
		High	**Low**

DOMAIN 4: Flow and Timing

Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Lunzer 1986

Study characteristics

Patient sampling	Cross-sectional, prospective, single centre study

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Lunzer 1986 *(Continued)*

	All pregnant women attending 1 hospital between March 1981 and December 1982 were asked to participate (total number not provided).
	297 pregnant women were enrolled. They were followed up during pregnancy with at least 5 visits, which included clinical evaluation and serum testing for glycocholic acid (GCA) and liver biochemistry tests. The clinical evaluation assessed if cholestatic symptoms, intake of drugs or pruritus were present. There were no women with known hepato-biliary, intestinal, pancreatic disease or with history of alcohol abuse.
Patient characteristics and setting	Setting: Royal North Hospital (Australia)
	Characteristics of patients: they were 16 to 42 years old, and their ethnicity was most often Mid-European (267 women), Mediterranean or Asian.
Index tests	Glycocholic acid (GCA). Assessed on serum sample, taken at a post-prandial status (2 h after a standard meal with 18 g of fat).
	Laboratory technique: radioimmunoassay (Abbott Diagnostics, North Chicago,III) (see notes)
	Diagnostic cut-off values: GCA > 1.5 µmol/L (see notes)
Target condition and reference standard(s)	ICP and follow-up during pregnancy with at least 5 visits, including clinical evaluation by the obstetrician and laboratory testing for glycocholic acid (GCA) and liver biochemistry tests. A decrease in serum glycocholic acid levels was assessed in all women 48 or 72 hours after delivery.
	NB: The assessment of raised GCA levels (the index test of the study) was included in the reference standard (see notes).
	The index test was part of the reference standard, assessed by obstetricians.
Flow and timing	Included pregnant women were assessed for pruritus and glycocholic acid after week 28 of pregnancy. They were followed up during pregnancy with multiple visits and until 48 or 72 hours after delivery to assess GCA levels reduction.
Comparative	
Notes	• The laboratory technique used to assess glycocholic acid has "a cross reactivity with taurocholic acid (16.5%) and glycochenodeoxycholic acid (14.5%)", which may affect the laboratory results. • The diagnostic cut-off value was determined after a preliminary study on 50 age-matched non-pregnant women, whose normal range of GCA was found to be 0 to 1.5 µmol/L. • All women were evaluated for cholestatic symptoms, pruritus, liver biochemistry tests and glycocholic acids during at least 5 visits during pregnancy. • 31 women showed raised levels of GCA and 69 women claimed for pruritus (15 among women with raised GCA, 54 among women with normal GCA). • The reference standard for ICP was the clinical evaluation showing both presence of pruritus and raised GCA levels, which decreased 48 or 72 hours after delivery.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

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Lunzer 1986 *(Continued)*

Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**

DOMAIN 2: Index Test Component(s) of serum bile acid profile

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
Was the index test not part of the reference standard?	No		
		High	**High**

DOMAIN 4: Flow and Timing

Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
		Low

Roger 1994

Study characteristics

Patient sampling	Case-control, prospective, multicentric study
	Among the 3192 pregnant women who attended 2 hospitals between 1 November 1988 and 31 October 1989, 51 of them were claiming for pruritus during pregnancy or immediately post-partum (< 7days) without previous other dermatological or systematic diseases. After the exclusion of 2 women, whose pruritus was unrelated to pregnancy, 49 women were enrolled in the study, and divided in different groups according to their final diagnosis.

Roger 1994 *(Continued)*

	Case group was represented by 17 women who were diagnosed with "pruritus gravidarum". These women were matched with 17 healthy pregnant controls taken by random sampling from excluded women with uncomplicated pregnancy.
	As the definition of "pruritus gravidarum" provided by the study matched our definition of ICP (see notes), we included the 17 woman with this diagnosis as patients. Their 17 matched controls were included as well.
	The prevalence of "pruritus gravidarum" as defined by article was 0.53%.
Patient characteristics and setting	Setting: Hôpital Trousseau and Hôpital Bretonneau and Beffroi, Tours (France)
	All participants were at their 26th to 40th week of pregnancy and there were 5 multiple and 12 singleton pregnancies in both groups.
Index tests	Total serum bile acids (TSBA), performed in all participants, and glycocholic acid (GCA), performed in all controls and 12 patients.
	Both index tests were assessed at the time of onset of symptoms.
	Laboratory technique:
	• Enzymatic assay according to Mashige et al (Mashige 1976) for TSBA • Immunoenzymatic for GCA
	Predefined diagnostic cut-off values: TSBA > 6 µmol/L, GCA > 0.7 µg/L
	Further information not available in the publication and Individual participant data were received from authors (see notes).
Target condition and reference standard(s)	ICP (see notes) and clinical evaluation including laboratory serum testing and liver ultrasounds to exclude other differential diagnosis and follow-up after delivery assessing spontaneous relief of pruritus (see notes). Reference standard assessed by obstetricians who were blind for the index test.
Flow and timing	Index test performed when the suspicion of disease arose in patients. All participants were at their 26th to 40th week of pregnancy. All participants underwent TSBA testing, while only 12 patients and all controls underwent GCA testing. A follow-up after delivery assessed the spontaneous relief of symptoms in all patients (information received from authors, see notes)
Comparative	
Notes	We received from Denis Roger (see study references) the full-text paper of the study, where we took into account the following information:
	1. Unpublished criteria for the diagnosis of "pruritus gravidarum":
	• pruritus with or without jaundice • absence of any "evolutive dermatosis" • absence of pre-existing or intercurrent liver disease • absence of pre-existing or intercurrent liver disease systemic disease (except for diabetes and hypertension in pregnancy) • facultative criteria: abnormal levels of TSBA or liver tests, but with negative serology for viral liver diseases
	2. The diagnostic criteria were assessed through a clinical evaluation including drug intake history, laboratory serum tests and liver ultrasounds.
	3. A follow up after delivery assessed the spontaneous relief of symptoms in all patients.
	4. The diagnostic cut-off values for the index tests were: TSBA > 6 µmol/L, GCA > 0.7 µg/L.
	5. TSBA were performed in all participants, while GCA only in 12 patients and all controls.

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Roger 1994 *(Continued)*

6. Individual participant data.

The criteria for the diagnosis of "pruritus gravidarum" described above, match our protocol definition of ICP. Thus, we decided to include these women as patients diagnosed with ICP.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	Yes		
		High	Low
DOMAIN 2: Index Test Total serum bile acids			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 2: Index Test Component(s) of serum bile acid profile			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowl-	Yes		

Total serum bile acids or serum bile acid profile, or both, for the diagnosis of intrahepatic cholestasis of pregnancy (Review)   **69**

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Roger 1994 *(Continued)*
edge of the results of
the index tests?

Was the index test not part of the reference standard?	Yes

	Low	Low

DOMAIN 4: Flow and Timing

Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes

	Low

Sjovall 1966

Study characteristics	
Patient sampling	Case-control, prospective, single centre study.
	6 pregnant women with generalised pruritus in the last trimester of pregnancy, 1 of whom had jaundice, were enrolled as patients with "pruritus in pregnancy" (see notes).
	22 pregnant women defined as "healthy" were enrolled as controls.
Patient characteristics and setting	Setting: Karolinska Institute - Department of Obstetrics and Gynaecology, Stockholm, Sweden
	Characteristics of control group not specified in the publication (said only they were "healthy")
Index tests	Total serum bile acid (TSBA), cholic acid (CA), chenodeoxycholic acid (CDCA), deoxycholic acid (DCA). All index tests were performed on serum fasting samples.
	Index tests were assessed once (at the time of onset of pruritus, week 30 to 38) in 4 patients, twice in 1 patient (week 38 and 39), 4 times (weeks 34, 38, 39, 40) in 1 patient, and once (week 14 to 39) in most controls. We considered for all patients and controls only the first assessment.
	Laboratory technique: gas-liquid chromatography
	Predefined diagnostic cut-off values: not provided for any index test
Target condition and reference standard(s)	ICP and clinical evaluation including follow-up after delivery assessing spontaneous relief of pruritus. Not provided any information about other liver tests assessments during pregnancy (except for 3 patients) and if/how other possible liver or skin diseases which could explain pruritus were ruled out (see notes).
Flow and timing	Index tests were assessed once (at the time of onset of pruritus, week 30 to 38) in 4 patients, twice in 1 patient (week 38 and 39), 4 times (weeks 34, 38, 39, 40) in 1 patient, and once (week 14 to 39) in most controls. We considered for all patients and controls only the first assessment. A follow-up after delivery assessed spontaneous relief of pruritus in all 6 patients (within 1 week after delivery), while the normalisation of liver tests was checked only in 2 patients.

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Sjovall 1966 *(Continued)*

Comparative	

Notes	The publication is entitled "Serum bile acid levels in pregnancy with pruritus". No information was provided about liver tests assessments during pregnancy (except for 3 patients) and if/how other possible liver or skin diseases which could explain pruritus were ruled out. However, authors associated the study patients with women diagnosed with "idiopathic jaundice of pregnancy" or "recurrent jaundice of pregnancy", "endogenous hepatotoxaemia of pregnancy", or "hepatosis of pregnancy", which were all the old names for ICP between the 1930s and 1960s. In addition, after their findings, they write in the discussion that "serum bile acid pattern in pregnant women with pruritus is therefore in agreement with the results of other liver function tests and histologic findings which indicate that this condition is associated with cholestasis".
	Moreover, this study is one of the most cited among publications on ICP to support the use of bile acids for the diagnosis of the disease.
	Therefore, despite the scanty information provided by the publication on participants' characteristics and how they were tested, we decided to include this study in our review as it seems to match our review question.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	Unclear		
		Unclear	**Unclear**
DOMAIN 2: Index Test Total serum bile acids			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
		Unclear	**Unclear**
DOMAIN 2: Index Test Component(s) of serum bile acid profile			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		

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Sjovall 1966 *(Continued)*

		High	Unclear
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
Was the index test not part of the reference standard?	Yes		
		Unclear	Unclear
DOMAIN 4: Flow and Timing			
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
		High	

Sun 2011

Study characteristics	
Patient sampling	Case-control, retrospective, single centre study
	The study enrolled pregnant women attending 1 hospital between October 2008 and May 2009.
	55 pregnant women were enrolled as patients with ICP, while 50 "healthy" pregnant women were enrolled as controls.
Patient characteristics and setting	Setting: Henan Oil Field Hospital (China)
	Characteristics of patients in case group: 21 to 34 years old, in their 28th to 38th week of pregnancy
	Characteristics of patients in control group: 20 to 28 years old, in their 20th to 30th week of pregnancy
	The different gestational age between groups may not lead to comparability of obtained results.
Index tests	Total serum bile acids
	Predefined diagnostic cut-off value: 20 µmol/l
	Laboratory technique: enzymatic colorimetric assay (automatic analyzer Aeroset 2000)
	Provided sensitivity: 87.5%. Provided specificity: 91.2 %

Sun 2011 *(Continued)*

Target condition and reference standard(s)	ICP and diagnostic criteria provided by a Chinese obstetrics and gynaecology book (see notes), assessed by obstetricians who were not blind for the index test.
Flow and timing	Total serum bile acids were performed at the time of onset of symptoms in patients. Follow-up after delivery assessing normalisation of signs and symptoms was part of the reference standard (see notes).
Comparative	
Notes	ICP was diagnosed following criteria provided by the Chinese obstetrics and gynaecology book 曹泽毅．中华妇产科学．人民卫生出版社 [Cao Zeyi. *Chinese Obstetrics and Gynecology*. People's Health Publishing House] 1999; 501-507. We were helped by Ms Maoling Wei to translate the paragraph concerning diagnostic criteria for ICP, which were:

- skin itching during pregnancy;
- abnormal liver function, mainly in serum transaminase elevation, alanine aminotransferase, aspartate aminotransferase increased at about 100 UI/L, seldom at 200 UI/L;
- some patients may demonsrate mild jaundice, serum bilirubin level at about 1.1 to 5mg/dl;
- patient without other obvious symptoms, such as vomiting, poor appetite and weak, etc.;
- once in labour, itching quickly subsided, liver function rapidly recovered to normal;
- elevation of creatine.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	Unclear		
		Unclear	**Unclear**
DOMAIN 2: Index Test Total serum bile acids			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		

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Sun 2011 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
Was the index test not part of the reference standard?	Yes		
		Unclear	**Low**

DOMAIN 4: Flow and Timing		
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
	Low	

Tripodi 2015

Study characteristics	
Patient sampling	All 5 publications cited under the reference ID Tripodi 2015 (Included studies section) were based on the database we received by email from Valeria Tripodi (see notes).
	Case-control, prospective, single centre study.
	Between January 2004 and June 2005, all pregnant women attending 1 hospital in their second half of pregnancy were screened for inclusion.
	Cases: 45 woman diagnosed with ICP for having pruritus, elevated aminotransferases, total serum bile acids > 11 μmol/l, absence of other known diseases (infectious, autoimmune, or skin diseases, alcohol intake, biliary obstruction). They all received UDCA treatment.
	Controls. 30 women among those clinically defined as healthy, were enrolled as controls.
	The calculated prevalence of ICP was 1.04%.
Patient characteristics and setting	Setting: Hospital JM Penna, Argentina (2596 yearly deliveries, thus meaning about 3894 estimated deliveries in the 18 months considered)
	Characteristics of patients in case group: 27.3 ± 1.0 years old, pre-selected for having total serum bile acids > 11 μmol/L
	Characteristics of patients in control group: 26.1 ± 1.4 years old
Index tests	Total serum bile acid, lithocholic acid (LCA), chenodeoxycholic acid (CDCA), deoxycholic acid (DCA), cholic acid (CA), ursodeoxycholic acid (UDCA), total tauro-conjugated/total glyco-conjugated bile acids (T-c/G-c). For TSBA, we received individual participant data (see notes).
	Laboratory technique: micellar electrokinetic chromatography with UV detection, on fasting serum sample
	Predefined diagnostic cut-off values
	• Total serum bile acids > 11 μmol/l

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Tripodi 2015 *(Continued)*

	• Not provided for the other index tests

Target condition and reference standard(s)	ICP and clinical evaluation including assessment of normalisation of symptoms and liver tests after delivery. Reference standard assessed by obstetricians, who were not blind for the index test as it was part of their evaluation
Flow and timing	Assessment of total serum bile acids after onset of symptoms in all patients. Follow-up assessing normalization of symptoms and liver biochemistry abnormalities after delivery in all patients.
Comparative	
Notes	We received further information on the study and a complete database from which all participant data were taken by email from Valeria Tripodi (see Included studies).
	One of the publications defined the study design as 'cross-sectional' but, following its design description and data received from authors, CM and TS agreed in defining it as 'case-control'.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	No		
		High	High
DOMAIN 2: Index Test Total serum bile acids			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 2: Index Test Component(s) of serum bile acid profile			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
		Low	Low
DOMAIN 3: Reference Standard			

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Tripodi 2015 *(Continued)*

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
Was the index test not part of the reference standard?	No		
		High	**Low**

DOMAIN 4: Flow and Timing

Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
	Low

ALT: alanine aminotransferase; AST: aspartate aminotransferase: CA: cholic acid; CDCA: chenodeoxycholic acid; CM: Cristina Manzotti (study author); DCA: deoxycholic acid; fCA: free (non-conjugated) cholic acid; fCDCA: free (non-conjugated) chenodeoxycholic acid; fDCA; free (non-conjugated) deoxycholic acid; fLCA: free (non-conjugated) lithocholic acid; G-c: total glyco-conjugated bile acids; GCA: glycocholic acid; GCDCA: glycochenodeoxycholic acid; GDCA: glycodeoxycholic acid; GLCA: glycolithocholic acid; GUDCA: glyco-conjugated ursodeoxycholic acid; LCA: lithocholic acid; RCOG: Royal College of Obstetricians and Gynaecologists; T-c Total tauro-conjugated bile acids; TCA: taurocholic acid; TCDCA: taurochenodeoxycholic acid; TDCA: taurodeoxycholic acid; TLCA: tauro-conjugated lithocholic acid; TS: Tea Stimac (study author); TSBA: total serum bile acids; TUDCA: tauro-conjugated ursodeoxycholic acid; UDCA: ursodeoxycholic acid.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abu-Hayyeh 2016	Lacking data. Authors did not sent additional data when asked by email.
Ai 2004	Lack of comparison with non-diseased pregnant women.
Almuna 1987a	Lacking data (only mean value ± 2SD of the index test results for women included as controls). Authors' contacts not found.
Ambros-Rudolph 2007	Lack of comparison with non-diseased pregnant women.
Anyikam 2013	Lack of comparison with non-diseased pregnant women.
Back 1974	No information on inclusion criteria for patients. Bile acid assessments performed on pooled serum samples and not on individual serum samples.
Bacq 1995	Lack of comparison with non-diseased pregnant women.
Bacq 1997	Lack of comparison with non-diseased pregnant women.

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Study	Reason for exclusion
Binder 2006	Lacking data (only mean value ± SD of the index test results for both diseased and non-diseased women). Further information received from T Binder (see study references), but data to complete a two-by-two table were not available.
Bouzouki 2013	Lacking data. Authors did not send additional data when asked by email.
Ch'ng 2003	Lacking data. Authors did not reply anymore during email correspondence.
Chen 2013	Lacking data. Authors refused to send additional data when asked by email.
Chianale 1982	Lacking data (only mean value ± SD of the index test results for both diseased and non-diseased women). No reply from authors.
Cowles 2005	Lacking data. No reply from authors contacted by email.
Dann 2004	Not matching the review question.
Dann 2005	Lacking data. Author's contact not found.
Favre 2010	Not maching the review question.
Garcia-Flores 2015	Incomplete reference standard (lack of follow-up after delivery).
Geenes 2012	Lacking data. Authors did not sent additional data when asked by email.
Glasinovic 1982	Lacking data (only mean value ± SD of the index test results for both diseased and non-diseased women). No reply from authors.
Heikkinen 1981	Lacking data (only mean value ± SD of the index test results for both diseased and non-diseased women). Authors' contacts not found.
Heikkinen 1983a	Lacking data (only mean value ± SD of the index test results for both diseased and non-diseased women). Authors' contacts not found.
Heikkinen 1983b	Lacking data (only mean value ± SD of the index test results for both diseased and non-diseased women). Authors' contacts not found.
Heikkinen 1983c	Lacking data (only mean value ± SD of the index test results for both diseased and non-diseased women). Author's contact not found.
Hong 2002	Lack of comparison with non-diseased pregnant women.
Hu 2015	Lacking data. No reply from authors.
Huang 2007	Not matching the review question.
Joutsiniemi 2008	Index test (TSBA) not performed in control group: values provided in the publication are reference laboratory values for healthy women (information received from authors, see study references).
Jurate 2017	Incomplete reference standard (lack of follow-up after delivery).
Kenyon 2001	Lack of comparison with non-diseased pregnant women.
Khan 2013	Lack of comparison with non-diseased pregnant women.

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Study	Reason for exclusion
Kirbas 2014	Index test (TSBA) not performed in control group.
Kremer 2015	Not matching the review question.
Laatikainen 1975	Lacking data (only mean value ± SD of the index test results for women included as controls). Authors' contacts not found.
Laatikainen 1977	Lacking data (only mean value ± SD of the index test results for women included as controls). Authors' contacts not found.
Laatikainen 1978	Lacking data (only mean value ± SD of the index test results for women included as controls). Authors' contacts not found.
Lee 2006	Incomplete reference standard (lack of follow-up after delivery).
Li 2013	Lack of comparison with non-diseased pregnant women.
Lisoni 1983	Lacking data (only mean value ± SD of the index test results for both diseased and non-diseased women). No reply from authors.
Lo 2007	Lack of comparison with non-diseased pregnant women.
Lopez 1982	Incomplete reference standard (lack of follow-up after delivery).
Madazli 2015	Lack of comparison with non-diseased pregnant women.
Mahey 2009	Lacking data. No reply from authors by email.
Meng 1997	Lacking data. No reply from authors by email.
Nezer 2017	Incomplete reference standard (lack of follow-up after delivery).
Oktaba 2013	Lack of comparison with non-diseased pregnant women.
Qu 2015	Index test (TSBA) not performed in control group.
Reyes 2006	Lacking data. Authors stopped to reply during an e
Samuelson 1980	Incomplete reference standard (lack of follow-up after delivery).
Sargın Oruç 2014	Lacking data. No reply from authors by email.
Sarria 1988	Lack of comparison with non-diseased pregnant women.
Shaw 1982	Lack of comparison with non-diseased pregnant women.
Subramaniam 2005	Lacking data. Authors' contacts not found.
Tribe 2010	Lacking data.
Yang 2014	Lacking data. No reply from authors by email.

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D A T A

Presented below are all the data for all of the tests entered into the review.

Table Tests. Data tables by test

Test	No. of studies	No. of partici-pants
1 TSBA (all studies)	13	1645
2 TSBA cut-off=10 µmol/L	11	839
4 CA cut-off=2 µmol/L	4	312
5 CA cut-off=3 µmol/L	4	312
6 CA cut-off=4 µmol/L	4	312
7 CA cut-off=5 µmol/L	4	312
8 CDCA cut-off=2 µmol/L	4	312
9 CDCA cut-off=3 µmol/L	4	312
10 GCA (all studies)	6	630
11 GCA cut-off=0.7 µmol/L	5	333
12 GCA cut-off=1.5 µmol/L	4	417
13 GCA cut-off=2 µmol/L	3	120
14 CA/CDCA cut-off=1.8	4	312
15 TSBA cut-off=10 µmol/L sensitivity excl TSBA in reference standard	5	497
16 TSBA cut-off=10 µmol/L sensitivity excl case-control	3	436

Test 1. TSBA (all studies).

Test 2. TSBA cut-off=10 µmol/L.

Test 4. CA cut-off=2 µmol/L.

Test 5. CA cut-off=3 µmol/L.

Test 6.   CA cut-off=4 µmol/L.

Test 7.   CA cut-off=5 µmol/L.

Test 8.   CDCA cut-off=2 µmol/L.

Test 9.   CDCA cut-off=3 µmol/L.

Test 10.   GCA (all studies).

Test 11.   GCA cut-off=0.7 µmol/L.

Test 12.   GCA cut-off=1.5 µmol/L.

Test 13.   GCA cut-off=2 µmol/L.

Test 14.   CA/CDCA cut-off=1.8.

Test 15.   TSBA cut-off=10 µmol/L sensitivity excl TSBA in reference standard.

Test 16.   TSBA cut-off=10 µmol/L sensitivity excl case-control.

ADDITIONAL TABLES

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

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Table 1.   Characteristics of included studies - Summary

Author	Year	Country	#	Study design	ICP definition	Index test(s)	Cut-off (µmol/l)^a	Laboratory technique	Timing
Almuna R	1986	Chile	241	case-control	Only clinical/with FU	GCA	0,7	Immunoenzymatic assay	Onset
Almuna R	1987	Chile	22	case-control	Clinical + lab/with FU	GCA	0,7	Immunoenzymatic assay	Delivery
Brites D *	1998	Portugal	77	case-control	Clinical + lab + TSBA/with FU	TSBA	10	Enzymatic fluorimetric	Onset
						CA§	not given	HPLC	Onset
						CDCA§	not given	HPLC	Onset
						GCA	not given	HPLC	Onset
						CA/CDCA§	not given		
Brites D *	1998	Portugal	14	case-control	Clinical + lab + TSBA/with FU	TSBA	10	Enzymatic fluorimetric	Delivery
						CA§	not given	HPLC	Onset
						CDCA§	not given	HPLC	Onset
						GCA	not given	HPLC	Onset
						CA/CDCA§	not given		
Gonzalez MC	1989	Chile	62	Cross-sectional	Clinical + lab + TSBA/with FU	TSBA	10	Enzymatic assay	Onset
Guducu N*	2013	Turkey	33	case-control	Clinical + lab + TSBA/with FU	TSBA	10	Enzymatic assay	Peak
Huang W*	2009	USA	193	Cross-sectional	Clinical + lab/with FU	TSBA	10	LC-MS	Onset
						CA	not given	LC-MS	Onset
						CDCA	not given	LC-MS	Onset
						CA/CDCA	3,4		

Table 1. Characteristics of included studies - Summary (Continued)

Jiang Y	2012	China	700	case-control	Clinical + lab + TSBA/with FU	TSBA	11	Enzymatic colorimetric	Onset
Kowals-ka-Kanka A*	2013	Poland	73	case-control	Clinical + lab + TSBA/with FU	TSBA	11	Enzymatic colorimetric	Peak
Laatika-nen T	1984	Finland	177	case-control	Clinical + lab/with FU	TSBA	10	Enzymatic assay	Delivery
Lang T*	2012	UK	66	Cross-sectional	Clinical + lab/with FU	TSBA	14	Enzymatic colorimetric	Onset
Lunzer M	1986	Australia	297	case-control	Clinical + lab/with FU	GCA	1,5	Radioimmuno assay	Onset
Roger D*	1994	France	34	case-control	Only clinical/with FU	TSBA	6	Enzymatic assay	Onset
						GCA	0,7	Immunoenzymatic assay	Onset
Sjovall K*	1966	Sweden	28	case-control	Only clinical/with FU	TSBA	not given	Gas-liquid chromatography	Onset
						CA	not given	Gas-liquid chromatography	Onset
						CDCA	not given	Gas-liquid chromatography	Onset
						CA/CDCA§	not given		
Sun Y	2011	China	105	case-control	Clinical + lab/with FU	TSBA	20	Enzymatic colorimetric	Onset
Tripodi V*b	2006-2015	Argenti-na	83	case-control	Clinical + lab + TSBA/with FU	TSBA	10	Enzymatic assay	Onset

ICP - Intrahepatic cholestasis of pregnancy

*Studies with individual participant data (provided in the publications or received from authors by email)

§ The index test was calculated by review authors on the basis of individual participant data. See full-text for explanations

aCut-offs given in this table are those provided in the publications

bWe refer to all publications given under the study ID "Tripodi 2015" (see "References of included studies")

"Clinical": based on symptoms and physical examination

"lab": based on laboratory exams (e.g. liver tests, viral serology, autoimmunity biomarkers)

"with FU": comprising follow-up after delivery

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"without FU": follow-up after delivery not performed

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A P P E N D I C E S

Appendix 1. Search strategies

Database	Time span	Search strategies
Cochrane Hepato-Biliary Group Controlled Trials Register	6 May 2019	(((bile or cholic or CA or glycocholic or GCA or choliglycine or chenodeox*cholic or CDCA or deox*cholic or DCA or lithocholic or LCA or ursodeox*cholic or UDCA or glyco-conjugated or tauro-conjugated or glycine or taurine) and acid*) AND ((cholestas* and (hepat* or liver*)) or jaundice or icterus graviardum) AND (pregnan* or obstetric* or gestation*)
Cochrane Hepato-Biliary Group Diagnostic Test Accuracy Studies Register	6 May 2019	(((bile or cholic or CA or glycocholic or GCA or choliglycine or chenodeox*cholic or CDCA or deox*cholic or DCA or lithocholic or LCA or ursodeox*cholic or UDCA or glyco-conjugated or tauro-conjugated or glycine or taurine) and acid*) AND ((cholestas* and (hepat* or liver*)) or jaundice or icterus graviardum) AND (pregnan* or obstetric* or gestation*)
Cochrane Library	2019, Issue 5	#1 MeSH descriptor: [Bile Acids and Salts] explode all trees #2 ((bile or cholic or CA or glycocholic or GCA or choliglycine or chenodeox*cholic or CDCA or deox*cholic or DCA or lithocholic or LCA or ursodeox*cholic or UDCA or glyco-conjugated or tauro-conjugated or glycine or taurine) and acid*) #3 #1 or #2 #4 MeSH descriptor: [Cholestasis, Intrahepatic] explode all trees #5 (cholestas* and (hepat* or liver*)) or jaundice or icterus graviardum #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 Ovid	1946 to 6 May 2019	1. exp "Bile Acids and Salts"/ 2. ((bile or cholic or CA or glycocholic or GCA or choliglycine or chenodeox*cholic or CDCA or deox*cholic or DCA or lithocholic or LCA or ursodeox*cholic or UDCA or glyco-conjugated or tauro-conjugated or glycine or taurine) and acid*).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. ((cholestas* and (hepat* or liver*)) or jaundice or icterus graviardum).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] 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 Ovid	1974 to 6 May 2019	1. exp bile acid/ 2. ((bile or cholic or CA or glycocholic or GCA or choliglycine or chenodeox*cholic or CDCA or deox*cholic or DCA or lithocholic or LCA or ursodeox*cholic or UDCA or glyco-conjugated or tauro-conjugated or glycine or taurine) and acid*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 3. 1 or 2

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		4. exp intrahepatic cholestasis/ 5. ((cholestas* and (hepat* or liver*)) or jaundice or icterus graviardum).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 6 May 2019	#4 #1 AND #2 AND #3 #3 TS=(pregnan* or obstetric* or gestation*) #2 TS=((cholestas* and (hepat* or liver*)) or jaundice or icterus graviardum) #1 TS=((bile or cholic or CA or glycocholic or GCA or choliglycine or chenodeox*cholic or CDCA or deox*cholic or DCA or lithocholic or LCA or ursodeox*cholic or UDCA or glyco-conjugated or tauro-conjugated or glycine or taurine) and acid*)
Conference Proceedings Citation Index – Science (Web of Science)	1900 to 6 May 2019	#4 #1 AND #2 AND #3 #3 TS=(pregnan* or obstetric* or gestation*) #2 TS=((cholestas* and (hepat* or liver*)) or jaundice or icterus graviardum) #1 TS=((bile or cholic or CA or glycocholic or GCA or choliglycine or chenodeox*cholic or CDCA or deox*cholic or DCA or lithocholic or LCA or ursodeox*cholic or UDCA or glyco-conjugated or tauro-conjugated or glycine or taurine) and acid*)
BIOSIS Previews (Web of Science)	1969 to 6 May 2019	#4 458 #1 AND #2 AND #3 #3 406,795 TS=(pregnan* or obstetric* or gestation*) #2 26,078 TS=((cholestas* and (hepat* or liver*)) or jaundice or icterus graviardum) #1 464,139 TS=((bile or cholic or CA or glycocholic or GCA or choliglycine or chenodeox*cholic or CDCA or deox*cholic or DCA or lithocholic or LCA or ursodeox*cholic or UDCA or glyco-conjugated or tauro-conjugated or glycine or taurine) and acid*)
CINAHL (EBSCOhost)	1981 to 6 May 2019	S14 64 S6 AND S9 S9 167,584 S7 OR S8 S8 167,584 TX pregnan* or obstetric* or gestation* S7 99,820 MW Pregnancy S6 2,167 S4 OR S5 S5 2,104 TX (cholestas* and (hepat* or liver*)) or jaundice or icterus graviardum S4 149 MW Intrahepatic Cholestasis S3 3,538 S1 OR S2 S2 3,538 TX (bile OR cholic glycocholic OR GCA OR choliglycine OR chenodeox?cholic OR CDCA OR deox?cholic OR DCA OR lithocholic OR LCA OR ursodeox?cholic OR UDCA OR glyco?conjugated OR tauro?conjugated OR glycine OR taurine) S1 412 MW Bile Acids and Salts
CNKI (Chinese database)	1979 to May 2019	((bile acid OR bile) AND pregnancy) OR ICP
VIP (Chinese database)	1989 to May 2019	(bile AND pregnancy) AND diagnosis
LILACS (VHL)	6 May 2019	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

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gestacional OR obstétrica)))) OR (tw:((tw:(ictèrícia)) 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"))

SCIELO	6 May 2019	1. ((cholestasis) AND (pregnancy OR obstetric)) OR ((colestasis) AND (embarazo OR ob-stétrica)) 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 gravidi-ca)
Evidence search: Health and Social Care, RHL, TRIP, OpenSIGLE, NTIS	6 May 2019	cholestasis AND (obstetric OR pregnancy) AND (bile acid)

Appendix 2. QUADAS-2

Domain	Participant selection	Index test	Reference standard	Flow and timing
Descrip-tion	**Describe methods of partic-ipant selection: describe in-clusion criteria for partic-ipants (prior testing, pre-sentation, intended use of index test, and setting):** The studies that fulfil the in-clusion criteria of this review should have included as par-ticipants pregnant women recruited in any clinical set-ting. They should have been eval-uated for personal history of skin or liver diseases, pres-ence of pruritus during their pregnancy, and they should have been assessed with any most common liver test (or tests), followed by any of the already mentioned index tests (total bile acids, cholic acid, glycocholic acid, chen-odeoxycholic acid, cholic/ chenodeoxycholic acid ratio, deoxycholic acid, lithocholic acid, ursodeoxycholic acid, total glyco-conjugated bile acids, total tauro-conjugat-ed bile acids, total glyco-con-jugated bile acids/total tau-	**Describe the index test and how it was be con-ducted and interpreted:** Total bile acids, cholic acid, glycocholic acid, chenodeoxycholic acid, cholic/chenodeoxycholic acid ratio, deoxycholic acid, lithocholic acid, ur-sodeoxycholic acid, to-tal glyco-conjugated bile acids, total tauro-conju-gated bile acids, total gly-co-conjugated bile acids/ total taurine-conjugated bile acids ratio, are non-invasive laboratory serum tests performed after the first clinical evaluation of the pregnant women for the diagnosis of intrahep-atic cholestasis of preg-nancy. The serum concen-tration of the index test(s) can be assessed through different techniques. Lab-oratory methods and diag-nostic cut-off values could vary between different studies.	**Describe the reference standard and how it was conducted and in-terpreted:** Clinical evaluation in-cluding the follow-up after delivery. The clin-ical evaluation is the final judgment of the clinician who takes into account the clinical as-sessment of suggestive signs and symptoms for intrahepatic cholestasis of pregnancy and the presence of any other-wise unexplained, per-sistent abnormalities of AST, ALT, or bilirubin levels until delivery. The follow-up after deliv-ery is the assessment of spontaneous relief of symptoms and nor-malisation of liver tests within eight weeks at most.	**Describe any people who did not receive the index test(s) or reference stan-dard (or both) or who will be excluded from the 2 x 2 table (refer to flow dia-gram): describe the time interval and any interven-tions between index test(s) and reference standard:** As mentioned in the proto-col, we will exclude partici-pants who lack data for the two-by-two table. To define a time interval be-tween our index tests and our reference standard is not relevant, as the index tests should be performed when the suspicion of intrahepat-ic cholestasis of pregnancy arises and the reference stan-dard comprises the follow-up after delivery.

rine-conjugated bile acids ra-
tio)

Sig-nalling ques-tions: yes/no/unclear	Was a consecutive or random sample of participants enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to classify the target condition correctly?	Was there an appropriate interval between index test(s) and reference standard?
	Yes: all consecutive participants or random sample of people with suspected intrahepatic cholestasis of pregnancy were enrolled in the study.	We think this will not be a relevant question for our review as the index tests are objective laboratory tests and the answer should always be 'Yes'.	Yes: if participants underwent a through clinical evaluation excluding all possible differential diagnosis 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.	This is not a relevant question to our review (see above).
	No: selected participants were not included.		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.		Unclear: insufficient data were reported to permit a judgement.	
	Was a case-control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all participants receive the reference standard?
	Yes: case-control design was avoided.	Yes.	Yes: clinical evaluation including the follow-up after delivery was performed without knowledge of the results of total serum bile acids or any component of serum bile acid profile.	Yes: all participants underwent the reference standard, i.e., clinical evaluation including the follow-up after delivery.
	No: case-control design was not avoided.	No.		No: not all participants underwent the reference standard, i.e., clinical evaluation including the follow-up after delivery.
	Unclear: insufficient information was reported to permit a judgement.	Unclear: it is not reported or not clearly described.	No: clinical evaluation including the follow-up after delivery was performed with knowledge of the results of total serum bile acids or any component of serum bile acid profile.	Unclear: insufficient data were reported to permit a judgement.
	Did the study avoid inappropriate exclusions?			Did all participants receive the same reference standard?
	Yes: the study avoided inappropriate exclusions (e.g., women having a previously assessed value of the index test(s) below a defined cut-off).		Unclear: insufficient data were reported to permit a judgement.	Yes: all participants received the same reference standard, i.e., clinical evaluation including the follow-up after delivery.

(Continued)

		Was the index test evaluation not part of the reference standard?	No: not all participants received the same reference standard, i.e., clinical evaluation including the follow-up after delivery.
No: the study excluded participants inappropriately. Unclear: insufficient data were reported to permit a judgement.		Yes: the index test evaluation was not part of the reference standard. No: index test evaluation was part of the reference standard. Unclear: insufficient data were reported to permit a judgement.	Unclear: insufficient data were reported to permit a judgement. **Were all participants included in the analysis?** Yes: all participants meeting the selection criteria (selected participants) were included in the analysis, or data on all the selected participants were available so that a 2 x 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 x 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 have introduced bias. Low risk of bias: no, if the selection of participants have not introduced bias. Unclear risk of bias: insufficient data on participants selection were reported to permit a judgement on the risk of bias.	**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 is 'no'. Low risk of bias: if the answer to the signalling questions on the conduct or interpretation of the index test is 'yes'. Unclear risk of bias: if the answers to the two signalling questions on the conduct or interpretation of the index test is either 'unclear' or any combination of 'unclear' with 'yes' or 'no'.	**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 is 'no'. Low risk of bias: if the answer to the signalling questions on the reference standard, its conduct, or its interpretation is 'yes'. Unclear risk of bias: if the answers to the three signalling questions on the reference standard, its conduct, or its interpretation is either 'unclear' or any	**Could the participant flow have introduced bias?** High risk of bias: if the answer to the signalling questions on flow and timing is 'no'. Low risk of bias: if the answer to the signalling questions on flow and timing is 'yes'. Unclear risk of bias: if the answers to the 4 signalling questions on flow and timing is either 'unclear' or any combination of 'unclear' with 'yes' or 'no'.

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			combination of 'un-clear' 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 is high concern that the included participants do not match the review question. Low concern: there is low concern that the included participants do not match the review question. Unclear concern: if it is unclear.	**Are there concerns that the index test, its conduct, or interpretation differ from the review question?** High concern: there is high concern that the conduct or interpretation of total serum bile acids or any component of serum bile acid profile differs from the way likely to be used in clinical practice. Low concern: there is low concern that the conduct or interpretation of total serum bile acids or any component of serum bile acid profile differs from the way likely to be used in clinical practice. Unclear concern: if it is 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 undergo clinical evaluation including the follow-up after delivery. Unclear concern: If it is unclear.	--

CONTRIBUTIONS OF AUTHORS

CM – formulated the research question, searched and selected the articles, extracted data, assessed quality, drafted the manuscript and reviewed the final version of the manuscript.

GC – provided statistical expert opinion, drafted part of the manuscript, involved in decision making, provided methodological and statistical analysis, and reviewed the final version of the manuscript.

TS – provided content expert opinion, searched and selected the articles, extracted data, assessed quality, and reviewed the final version of the manuscript.

DN – provided advice and suggestions, involved in decision making, corrected writing style and language, and reviewed the final version of the manuscript.

CG – provided methodological expert opinion, involved in decision making, and reviewed the final version of the manuscript.

All authors approved the final review for publication.

DECLARATIONS OF INTEREST

CM: none known
GC: none known
TS: none known
DN: none known
CG: none known

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Internal sources

- The Cochrane Hepato-Biliary Group, Denmark.
- CM's parents, Italy.

  Supported CM while working in Copenhagen at the CHBG Editrial Team office

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

At the protocol stage, we planned to analyse the accuracy of eleven index tests: total serum bile acids (TSBA), cholic acid (CA), glycocholic acid (GCA), chenodeoxycholic acid (CDCA), cholic/chenodeoxycholic acid ratio (CA/CDCA), deoxycholic acid (DCA), lithocholic acid (LCA), ursodeoxycholic acid (UDCA), 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). However, we analysed only the diagnostic accuracy of TSBA, CA, CDCA, CA/CDCA, GCA, and we did not perform the analysis over the accuracy of LCA, DCA, UDCA, G-c, T-c, G-c/T-c, as there were too few data available.

We decided not to analyse the accuracy of combinations of the index tests (that in our review protocol was defined as TSBA plus any component of serum bile acid profile) as none of the included studies did so. However, we will examine the possibility for doing this analysis in the future, based on the individual participant data we have assembled.

We analysed sources of heterogeneity only for TSBA with a cut-off of 10 µmol/L. Owing to the small number of studies, among the sources of heterogeneity planned at the protocol stage — 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 — we analysed only laboratory technique used, timing of assessment of the index tests, and therapy (if included patient received UDCA or not).

We have deleted LRs and predictive values from the Methods section; we estimated only sensitivity and specificity.

At the protocol stage, we planned to perform the following sensitivity analyses.

- 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).
- Excluding all studies with case-control design.
- Excluding only studies with case-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 standards.

However, we could not perform a sensitivity analysis excluding the studies at high risk of bias, as only one study was judged at low risk of bias in all domains. Moreover, all case-control studies enrolled asymptomatic pregnant women as controls; none of them included symptomatic pregnant women (i.e. with pruritus). Hence, we made only the other two planned sensitivity analyses (excluding case-control studies; and excluding studies where TSBA were part of the reference standard).

In the protocol, we planned to test for publication bias. However, considering that these statistical methods are not widely used in diagnostic test accuracy reviews, and also due to the lack of validated methods, we decided not to assess publication bias.

INDEX TERMS

Medical Subject Headings (MeSH)

Bile Acids and Salts [*blood]; Biomarkers [blood]; Cholestasis, Intrahepatic [*blood] [*diagnosis]; Diagnostic Tests, Routine; Pregnancy Complications [*blood] [*diagnosis]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy

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