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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Is ursodeoxycholic acid effective for intrahepatic cholestasis of pregnancy?

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Abstract

Intrahepatic cholestasis of pregnancy is a condition associated with fetal morbidity and mortality. Ursodeoxycholic acid has been proposed as a treatment alternative, but its use remains controversial. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified three systematic reviews including eight randomized trials. We combined the evidence using meta-analysis and generated a summary of findings table following the GRADE approach. We concluded ursodeoxycholic acid reduces prematurity risk and need for admission in neonatal intensive care units. It might also reduce maternal pruritus.

Problem

Intrahepatic obstetric cholestasis is an exclusive condition of pregnancy. The highest prevalence is in South America and Scandinavia, where it is about 6-29% [1]. It is characterized by the appearance of severe palmoplantar pruritus predominantly nocturnal, during the third trimester of pregnancy, which may be associated with elevated liver enzymes and bile acids. The etiology of this condition is not completely understood, but genetic, hormonal and environmental factors would be involved [2]. It has been associated to an increase in premature delivery, neonatal respiratory distress syndrome and spontaneous fetal death, among others.

Ursodeoxycholic acid could reduce symptoms and adverse outcomes decreasing hepatocellular damage and placental transfer of bile acids by replacing toxic endogenous bile acids without altering the biliary function[3],[4]. However, there is controversy about the real usefulness of this intervention.

Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information, we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages
- Ursodeoxycholic acid probably reduces prematurity risk and admission to neonatal intensive care unit in intrahepatic cholestasis of pregnancy.
- Ursodeoxycholic acid might decrease pruritus in women with intrahepatic cholestasis of pregnancy.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found three systematic reviews [5],[6],[7], including 14 studies reported in 21 references [8],[9],[10],[11], [12],[13],[14],[15],[16],[17],[18],[19],[20],[21],[22], [23],[24],[25],[26],[27],[28]. Eight studies corresponded to randomized controlled trials (15 references [9],[10],[11], [12],[13],[14],[16],[17],[19],[21],[22],[23],[24],[26],[27]). This table and the summary in general are based on the latter. One study [15] did not contribute data to any of the outcomes of interest.
What types of patients were included	All of the studies included pregnant women with clinical diagnosis of obstetric cholestasis. Six studies reported when pruritus started; in four studies started at week 29 [11],[12],[22],[23] and in two at week 24 [10],[17]. Five studies also used laboratory test results (bile acids > 10 and/or aminotransferase increase) as inclusion criteria [10],[11],[12],[17],[23]. Two studies did not describe inclusion criteria [14],[16]. Age and race were not considered as inclusion criteria in any study.
What types of interventions were included	All of the studies used oral ursodeoxycholic acid. Daily dose was different across studies: 600 mg [11],[22], 900 mg [16],[17], 1000 mg [12],[23], 500-2000 mg [10] and it was not specified in one study [14]. The intervention was administered during 14 days in two studies [16],[17], 20 or more days in three studies [11],[12],[22] and it was not specified in three studies [10],[14],[23]. All of the studies compared against placebo.
What types of outcomes were measured	Several outcomes were measured in the studies. The outcomes were divided in maternal outcomes (reduction of pruritus, aminotransferase and bile acid levels, cesarean section and adverse effects) and neonatal outcomes (prematurity, stillbirth, admission to neonatal intensive care unit, meconium staining of amniotic fluid, birth weight and fetal distress).

Summary of findings

The information on the effects of ursodeoxycholic acid in intrahepatic cholestasis of pregnancy is based on eight randomized controlled trials that included 363 patients. Four studies reported pruritus improvement[11],[12],[22],[23], six studies stillbirth [10],[11],[12],[14],[17],[23], six studies prematurity [10],[11],[12],[17],[22],[23] and four studies reported admission to neonatal intensive care unit [10],[11],[22],[23].

- Ursodeoxycholic acid might reduce pruritus in women with intrahepatic cholestasis of pregnancy. The certainty of the evidence is low.
- Ursodeoxycholic acid might reduce stillbirth risk in women with intrahepatic cholestasis of pregnancy. The certainty of the evidence is low.
- Ursodeoxycholic acid probably reduces prematurity risk in intrahepatic cholestasis of pregnancy. The certainty of the evidence is moderate.
- Ursodeoxycholic acid probably reduces admission to neonatal intensive care unit in intrahepatic cholestasis of pregnancy. The certainty of the evidence is moderate.

Ursodeoxycholic acid for intrahepatic cholestasis of pregnancy

Patients Women with clinical diagnosis of intrahepatic cholestasis of pregnancy
Intervention Ursodeoxycholic acid (UDCA)
Comparison Placebo

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT UDCA	WITH UDCA		
	Difference: patients per 1000			
Pruritus reduction	257 per 1000	527 per 1000	RR 2.05 (0.62 to 6.77)	⨁⨁◯◯[1,2,3] Low
	Difference: 270 patients more per 1000 (Margin of error: 98 less to 1000 more)			
Stillbirth	12 per 1000	4 per 1000	RR 0.31 (0.03 to 2.84)	⨁⨁◯◯[1,2] Low
	Difference: 8 less per 1000 (Margin of error: 12 less to 22 more)			
Prematurity	369 per 1000	151 per 1000	RR 0.41 (0.26 to 0.65)	⨁⨁⨁◯[4,5] Moderate
	Difference: 218 less per 1000 (Margin of error: 129 to 273 less)			
Admission to neonatal intensive care unit	151 per 1000	24 per 1000	RR 0.16 (0.03 to 0.89)	⨁⨁⨁◯[4,6] Moderate
	Difference: 127 less per 1000 (Margin of error: 17 to 147 less)			

RR: Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

* The risk **WITHOUT ursodeoxycholic acid** is based on the risk in the control group of the trials. The risk **WITH ursodeoxycholic acid** (and its margin of error) is calculated from relative effect (and its margin of error)

1 The certainty of the evidence was downgraded for risk of bias. All of the studies have serious or very serious limitations.
2 The certainty of the evidence was downgraded because of imprecision given the confidence interval includes the possibility of no effect.
3 We did not decrease the certainty of the evidence despite of inconsistency (I^2= 71%) because it is explained by one study where all patients, in both intervention and placebo groups, experienced and improvement in this outcome, so there was no possible difference.
4 We did not decrease the certainty of the evidence despite of risk of bias in some studies since the study with more weight in the meta-analysis had low risk of bias (PITCH study).
5 We downgraded the certainty of the evidence for inconsistency on the population of interest. Many patients were included outside the range of prematurity, so cannot be considered for the event. It is not possible to determine the impact on prematurity since the studies do not report the range of gestational age to delivery.
6 We downgraded the certainty of the evidence for risk of bias. This outcome is sensitive to performance bias given its subjective nature. It can be also suspected because there was no impact in other outcomes that are related such as general mortality.

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

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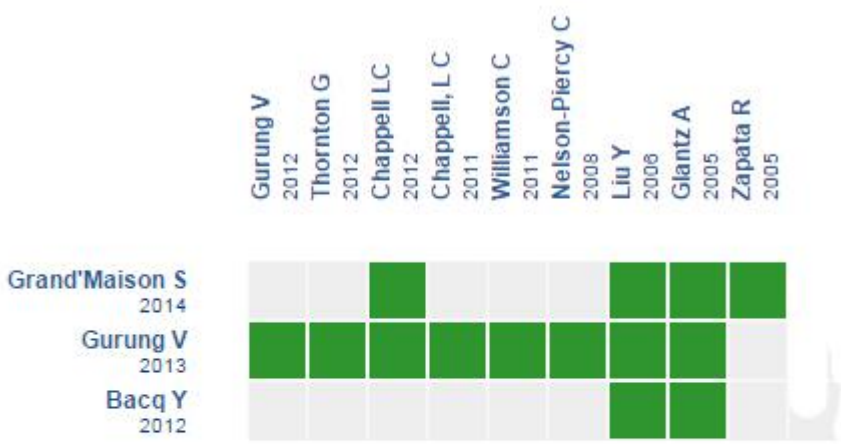
Other considerations for decision-making

To whom this evidence does and does not apply
• The evidence presented applies to women with clinical diagnosis of intrahepatic cholestasis of pregnancy. • The conclusion of this summary should not be extrapolated to pregnant women with hepatic and biliary diseases from a different etiology.
About the outcomes included in this summary
• Maternal outcomes (pruritus) and neonatal outcomes (stillbirth, premature delivery and admission to neonatal intensive care unit) critical for decision making according to the opinion of the authors were included in this summary. • Other surrogate outcomes like aminotransferase level reduction were not included in the summary of findings table, but also support the conclusion. (Without UDCA: 143 per 1000, with UDCA 410 per 1000; Difference: 267 patients more per 1000 [Margin of error: 91 to 577 more]; RR 2.87 [1.64 to 5.04]; Moderate certainty) [11],[12],[22],[23].
Balance between benefits and risks, and certainty of the evidence
• Although there is an important uncertainty for some outcomes, it is a safe intervention, so probably the risk-benefit ratio is favorable to the use of ursodeoxycholic acid.
What would patients and their doctors think about this intervention
• Considering it is a safe intervention with beneficial effects on the more relevant neonatal outcomes, it is likely that most patients and their doctors would choose to use the intervention. • It is particularly important to inform patients about the uncertainty about maternal outcomes.
Resource considerations
• Even though it is a moderately expensive intervention, given its effect on the main neonatal outcomes it is probably a cost-effective intervention.
Differences between this summary and other sources
• The conclusions of this summary are consistent with those of the identified systematic reviews. • The conclusions of this summary partially agree with the main guideline identified in terms of recommending the use of ursodeoxycholic acid. However, the justification differs, since this guideline states it reduces maternal pruritus but there is insufficient evidence on perinatal outcomes [29].
Could this evidence change in the future?
• The probability that new studies change the information presented in this summary is moderate, because of the certainty of the evidence. • Future evidence could improve the certainty for the outcome pruritus. There is at least one randomized trial published after the identified systematic reviews[29]. • There are no ongoing trials that could change what we know, at least according to the World Health Organization International Controlled Trials Registry Platform.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** Ursodeoxycholic acid versus placebo for intrahepatic cholestasis of pregnancy

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears. The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

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