

A Clinical & Experimental Obstetrics and Gynecology survey on ursodeoxycholic treatment of intrahepatic cholestasis of pregnancy: scholars' opinion

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The current paper reports a survey on intrahepatic cholestasis of pregnancy (ICP), concerning obstetric outcomes and treatment of the disease. The survey assessed the opinions of contributors on ursodeoxycholic acid (UDCA) therapy and ICP care. It was administered online on behalf of the editorial office of Clinical & Experimental Obstetrics and Gynecology. Ten questions were provided to the scholars, fellows and peers. Nine questions of the survey allowed closed answers, while the tenth question was open. Semantic Brand Score (<https://semanticbrandscore.com/>) was used to conduct the survey and to extract the key concepts on ICP. Despite the unclear roles of ursodeoxycholic acid in ICP, respondents believed that reducing the bile acid using ursodeoxycholic acid was beneficial to prevent adverse pregnancy outcomes. The three key-concepts frequently reported by respondents in the optional text responses were (1) disease severity, (2) need for research, and (3) management. In conclusion, respondents demonstrated a marked disparity in their understanding and use of ursodeoxycholic acid in ICP, highlighting the importance of urgent update of international guidelines, in the light of recent publications.

Keywords

Intrahepatic cholestasis of pregnancy; Ursodeoxycholic acid; Treatment; Outcome; Opinion; Survey

1. Introduction

Intrahepatic cholestasis of pregnancy is a common disorder in pregnancy manifested by pruritus and elevated levels of bile acid more common in the third trimester of gestation. Its aetiology is unclear and its treatment and outcome are still poorly supported by robust evidence-based data [1]. This is due to different conditions linked to the disease, able to cause heterogeneity in its behaviour. For example, genetic differences among at risk populations, maternal age, concurrent maternal disorders, multiple pregnancy or twins pregnancies after artificial reproductive treatments [2–5].

Ursodeoxycholic acid (UDCA) treatment in intrahepatic cholestasis of pregnancy (ICP) has been recommended in many international guidelines for the management of symptoms and prevention of adverse pregnancy outcomes [6]. However, conflicting data were published in 2019 regard-

ing the utility of administering UDCA for these symptoms [7, 8], and the risk of stillbirth associated with the condition was reported to be limited to women with the most severe disease [9]. Therefore, literature supporting the routine use of UDCA for improving pregnancy outcomes should be interpreted with a caveat. Despite this, many authors report that recent findings will not affect their policy for managing ICP with UDCA [10, 11]. Obstetricians, therefore, face the challenge of counselling women on pregnancy outcomes with or without UDCA treatment, where practice differs between clinicians.

The current short survey, on behalf of *Clinical & Experimental Obstetrics and Gynecology* Journal, aimed to assess the opinions of contributors on using UDCA for treatment of ICP, before publication of a recent individual participant data meta-analysis of Ovadia *et al.* [12]. The latter research would suggest that a mild improvement in some pregnancy outcomes occurrence is observed when treating with UDCA, thereby complicating the uncertainty of the available knowledge.

This paper discusses results of the survey.

2. Methods

Journal editors and clinicians managing obstetric patients were invited by the *Clinical & Experimental Obstetrics and Gynecology*, to participate in an online survey on ICP and treatment with UDCA. Additional respondents were reached through ResearchGate, personal e-mail contacts of the authors, and dissemination via Twitter. The survey started in December 2020 and closed on 30th April 2021, prior to publication of an individual participant data meta-analysis of UDCA in ICP [12]. The survey questions are listed in Table 1 (first column). Answers were closed for the first nine questions (answers permitted are listed in the second column of Table 1). The last question allowed open answers. The online survey was performed using SurveyMonkey (<http://www.surveymonkey.com/>). Respondents were anonymous.

Table 1. List of questions and rates of answers.

Questions	Answers	N – Rates (total n = 76)
(1) Do you believe that ursodeoxycholic treatment improves one or more outcomes of intrahepatic cholestasis of pregnancy?	-Yes	54–71.1%
	-No	7–9.2%
	-Not sure	15–19.7%
(2) Do you believe that ursodeoxycholic treatment improves one or more outcomes of intrahepatic cholestasis of pregnancy in case of severe disease (≥ 40 micromol/L of blood bile acid)?	-Yes	46–60.5%
	-No	9–11.8%
	-Not sure	21–27.6%
(3) Do you believe that ursodeoxycholic treatment improves one or more outcomes of intrahepatic cholestasis of pregnancy in case of mild disease (< 40 micromol/L of blood bile acid)?	-Yes	45–59.2%
	-No	14–18.4%
	-Not sure	17–22.4%
(4) Do you believe that ursodeoxycholic treatment reduces bile acid levels?	-Yes	57–75.0%
	-No	9–11.8%
	-Not sure	10–13.2%
(5) Do you believe that ursodeoxycholic acid improves itching sensation by the patients?	-Yes	53–69.7%
	-No	11–14.5%
	-Not sure	12–15.8%
(6) Do you believe that bile acid levels associate with adverse pregnancy outcomes in cases of intra-hepatic cholestasis of pregnancy?	-Yes	55–72.4%
	-No	9–11.8%
	-Not sure	12–15.8%
(7) Which adverse pregnancy outcomes could be improved by ursodeoxycholic treatment for intra-hepatic cholestasis of pregnancy?	-Non iatrogenic preterm delivery	8–10.5%
	-Iatrogenic preterm delivery	21–27.6%
	-Intrauterine fetal death	14–18.4%
	-Meconium stained amniotic fluid	5–6.6%
	-Fetal distress	5–6.6%
	-Placental abruption	0–0
	-Post partum haemorrhage/bleeding disorders	1–1.3%
	-Other	4–5.3%
	-No relationship among adverse outcomes and treatments	18–23.7%
(8) Have you changed your opinion on ursodeoxycholic treatment for pregnancy cholestasis recently (after the 2019 articles were published)?	-Yes	26–34.2%
	-No	38–50.0%
	-Not sure	12–15.8%
(9) Do you believe that other pharmacological treatments for intrahepatic cholestasis of pregnancy are available for improving pregnancy outcomes, besides ursodeoxycholic acid?	-Yes	31–40.8%
	-No	21–27.6%
	-Not sure	24–31.6%
(10) Please, state briefly what do you think about intrahepatic cholestasis of pregnancy.	Open answers	/

The multiple choice answers were collected, while the descriptive answers were assessed by Semantic Brand Score (SBS) web app [13] to identify the key concepts perceived by respondents. The SBS assesses words in a given set of texts to evaluate their importance and recurrent associations. The metric has its foundations in graph theory and combines methods of text mining and social network analysis. By assessing spontaneous disclosing of respondents (or short messages in social networks, newspapers, e-mails, etc), SBS is not affected by cognitive bias. In the current study, “ICP” was set as brand and the top textual brand associations in the spontaneous descriptive answers were assessed after removing stop-words and word affixes. Moreover, “intrahepatic cholestasis of pregnancy” and phrases with similar meaning were rewritten

as “ICP”. The same process was applied to the “ursodeoxycholic acid”, abbreviated to “UA”. English was set as the language for SBS analysis.

3. Results

Seventy-six respondents participated in the survey. Table 1 summarizes the results, with the majority responding that UDCA is beneficial for adverse pregnancy outcomes, reducing bile acid concentrations and improving pruritus. Only 34% (26/76) of respondents had altered their practice regarding UDCA treatment after reading the results of the 2019 clinical trial and the observational study reporting associations of adverse pregnancy outcomes with biochemical markers [9].

Fig. 1 reports the top textual associations between the acronym “ICP” and other words provided by respondents in the free text answer. This suggests three key-concepts were important for respondents with relation to current knowledge about ICP: (1) severity, (2) need for research, (3) management.

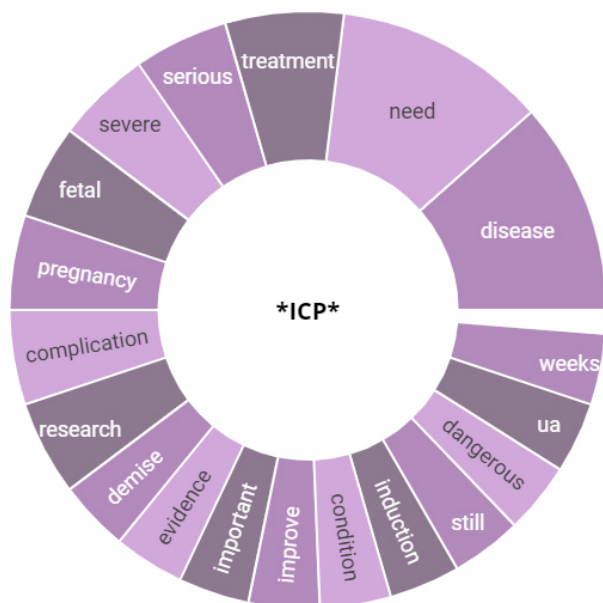


Fig. 1. SBS top textual brand associations. ICP stands for Intrahepatic Cholestasis of Pregnancy, and UA stands for ursodeoxycholic acid. The larger is the purple area, the higher the strength of the association of the word combinations with ICP. Words meaning and the strength of their association with ICP leads us to extract three key-concepts: (1) awareness of severity of the disease; (2) need for research, (3) management. Taken together, those key-concepts would reinforce the idea that many items on ICP are still unclear to respondents.

4. Discussion

By assessing the results of the survey, the disparity between respondents in their management of ICP and use of UDCA can be demonstrated. Our results suggest that the majority of respondents believe that UDCA treatment is of benefit for ICP because it reduces the bile acid. This is important due to the previous studies reporting associations between the adverse perinatal events and the levels of bile acid [14, 15].

Interestingly, UDCA treatment did not reduce total levels of the serum bile acid compared with placebo in the 2019 randomised clinical trial [7, 16], in which the number of patients recruited to the trial surpassed any previous placebo-controlled studies. Rather, high doses of UDCA would favour the removing of bile acids from the fetal compartment by up-regulating the Breast Cancer Resistance Protein (a bile acid carrier) expression in the placenta, authors have reported [17]. Within the limited confines of this survey, we were not able to elucidate whether respondents had an erroneous understanding of the mechanism of action of

UDCA, as the proven impact of UDCA treatment in ICP is altering the composition of the bile acid pool rather than a reduction in its total concentration [10, 18]. Additionally, some respondents may not yet be aware of the latest research, as it is well recognized that there is a marked delay between the acquisition of new scientific knowledge and implementation into clinical practice, a process that can be expedited by the relevant professional organisations [19].

It is interesting that half of respondents had not changed their practice in response to the 2019 clinical trial of UDCA. Whilst a number of meta-analyses had previously reported the overall benefits of UDCA treatment, alternative methods of statistical analyses provided conflicting results [20]. The 2019 study [7] included 605 participants and was placebo-controlled; this is more than four times larger than any previous trial of UDCA in ICP, and included more participants than the total number included in most comparisons from meta-analyses (the exception being results of UDCA effect on alanine aminotransferase (ALT) concentrations that included 662 participants) [21]. This may reflect an understanding of non-trial-based research studies in ICP reporting potential benefits of UDCA. For example, on fetal cardiomyocytes and at the placenta; due to perceived benefit of UDCA outside of the primary outcomes of the 2019 trial (for example in reduction of ALT, meconium-stained amniotic fluid and marginal reduction in pruritus). The inclusion criteria for the trial raised some concerns [10] such as the lack of awareness of the trial results. In addition, the findings of the study supported their previous practice in which UDCA had not been prescribed. This reveals a limitation in our fast survey approach with a limited number of questions, numbers and completion time is likely to improve the number of questionnaires completed, but at the expense of richness of response.

A reduction in iatrogenic preterm birth was among the benefits of UDCA treatment reported by the majority of respondents; presumably due to an assumption that UDCA treatment reduces the risk of stillbirth for which iatrogenic preterm birth is otherwise performed. To the best of our knowledge, no previous study has reported this benefit. However, the recent meta-analysis of individuals undergoing UDCA treatment in ICP has demonstrated that UDCA can reduce a composite outcome of preterm birth and stillbirth [12]. Whilst not evidence-based at the time, on this occasion the expert opinion of respondents may, indeed, prove correct in the long term.

The SBS results of the free text answers suggest the majority of the respondents believed that there is limited knowledge about the accepted management for ICP along with a fear of the adverse fetal outcomes associated with the disease. Remarkably, this knowledge is free from cognitive bias, underlining how pivotal an expertise-based approach to the ICP management is.

The main limitation of the study is that many information or respondents was not planned to be collected (position of respondents, country of origin, years of practicing, field of

expertise, etc.), aiming to have more respondents to the main questions listed above (Table 1). Nevertheless, it is of interest that personal opinion of such respondents is related with both knowledge and perception of the disease. Together, those items would address physicians to correctly manage ICP, in spite of the conflicting evidence-based medicine currently available.

5. Conclusions

The results of this fast survey, in combination with recent literature [7, 9, 12] reveal large disparities between the clinicians. As such, we suggest that evidence-based guidelines should be urgently updated to enable a greater standardization of care and optimization of prognosis of the affected women.

Author contributions

UI planned the study, organized the survey, performed calculations. CO and UI interpreted results and wrote the manuscript. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

UI declares no conflict of interest. CO is consultant for Mirum Pharmaceuticals. UI is serving as one of the Editorial Board members of this journal. We declare that UI had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to PC.

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