Diagnostic criteria for intrahepatic cholestasis of pregnancy: should the timing of total bile acids measurement be established?

Mor Huri[1], Camilla Lippi[1], Viola Seravalli[1], and Mariarosaria Di Tommaso[2]

[1]University of Florence
[2]Careggi Hospital University of Florence

September 7, 2022

Running title: Timing of total serum bile acids measurement

Title: Diagnostic criteria for intrahepatic cholestasis of pregnancy: should the timing of total bile acids measurement be established?

Huri Mor MD[1+], Lippi Camilla MD1[+], Seravalli Viola MD1 & Di Tommaso Mariarosaria MD PhD1

1Department of Health Sciences, Obstetrics and Gynecology Unit, University of Florence, Florence, Italy.

+ These authors have contributed equally to this work

Corresponding author

Di Tommaso Mariarosaria, MD, PhD.

Department of Health Sciences, Obstetrics and Gynecology Unit, University of Florence.

Largo Brambilla, 3, 50134, Florence, Italy, Email: mariarosaria.ditommaso@unifi.it.

Tel 0039-335332709

We welcome the updated guidelines from the Royal College of Obstetrics and Gynaecology for Intrahepatic Cholestasis of Pregnancy (ICP) diagnosis and management (Green-top Guideline No. 43 June 2022)[1]. We believe that the new recommendations, based on a recent body of evidence, will positively impact patients' care and the management of ICP.

The correlation with a potentially increased risk of stillbirth makes ICP a difficult obstetrics pathology to manage. Since it is strongly associated with maternal anxiety and active management, the diagnosis of ICP has serious implication, and therefore a correct diagnosis is essential.

While the previous edition of the guidelines (April 2011) recommended to apply the upper limit of pregnancy-specific ranges of total serum bile acids (TSBA) for diagnosis, an important innovation in the current guidelines is the accurate definition of the diagnostic threshold [2]. The new edition, based on a recent study by Mitchell et al [1], establishes for the first time the upper limit of 19 μmol/L for random measurement of TSBA. Mitchell et al, by retrospective analysis of non-fasting serum samples from a local database, determined the upper reference limit of TSBA in three ethnic groups. The authors proposed using the upper limit of the black ethnicity population, in order to avoid overdiagnosis and since no adverse events were associated with TSBA concentration below that threshold [3].

We regret that the new guidelines were published shortly after the publication of our cross-sectional study in which we aimed to establish reference standards for TSBA in pregnancy, and thereby could not include our paper. Our study used a prospective design and was based on the largest pregnant population so far

(612 patients). Interestingly, a very similar upper reference limit (20 μmol/l) of the postprandial TSBA measurement was found in the whole population that has been examined [4]. We believe that pregnancy-specific reference ranges should be used to identify patients with altered TSBA concentration within the pregnant population, and to better distinguish patients with mild ICP from those with moderate or severe ICP.

Having two independent studies that arrive at such a similar threshold may reinforce the new proposed diagnostic criteria and increase the level of evidence of the recommendation.

In the new edition of the Guidelines, the first key recommendation refers to TSBA random measurement for diagnosis of ICP. The authors then specify that bile acid measurements "should be taken at a convenient time, and do not need to be performed fasting". We would like to briefly comment the decision to use a random threshold for the diagnosis.

To understand ICP, we believe it is important to understand the relationship between fasting TSBA and postprandial TSBA in pregnant women. Following a meal, TSBA concentrations increase only slightly in healthy non-pregnant patients. However in the pregnant population, with and without ICP, TSBA concentrations significantly increase in response to food intake [3][4][5][6]. Postprandial TSBA measurements correspond to the peak concentration and are more likely to identify women with TSBA [?] 100 μmol/l, therefore at an increased risk of stillbirth [7].

Conversely, a random measurement may not correspond to the peak concentration, as TSBA peak at 60-90 minutes and then return to fasting levels [8]. For example, a random concentration of 18 μmol/l could be a peak value in a patient with gestational pruritus according to the new guidelines, but it could also be closer to the fasting concentration, and thereby a potential diagnosis of ICP would be missed.

Our study suggests that two different reference ranges should be used, one for each timepoint (fasting [?] 14 μmol/l, postprandial [?] 20 μmol/l). The physician should consider at which timepoint the measurement was taken in order to interpret the results correctly. By prescribing a random measurement, the patient is usually requested to perform the blood sample at any moment during the day: which can be 5 hours postprandialy, shortly after a meal, or in cases of inadequate communication, together with other blood test that requested fasting.

It is important to specify that the postprandial sample should be drowned 2-3 hours after a meal. Just like the glucose challenge test should be performed in a very specific timeline, since a random glycaemic stick would diagnose gestational diabetes with difficulty. We believe that the measurement of TSBA should be standardized too, based on the current literature.

We agree that the peak measurement is more clinically relevant, and essential for the diagnosis and severity assessment of ICP. We believe, however, that at least one measurement of fasting TSBA, together with postprandial assessment, should be performed in the initial workup for ICP. High fasting concentrations are more specific for ICP, as suggested previously [5][6][9]. Fasting measurement are also more predictable, have less variability, and correlate better with certain risk factors. The postprandial peak measurement should be repeated for risk stratification and for the follow-up of patients diagnosed with ICP, to guide the management of the pregnancy and the timing of delivery.

We are happy to see the attention that this topic has recently received and the continuation of this important debate regarding the diagnostic criteria, that have important implication for maternal, fetal and neonatal health. We congratulate the RCOG on their important new recommendations that will benefit pregnant patients worldwide.

Keywords: Intrahepatic cholestasis of pregnancy; Total serum bile acids; Diagnostic thresholds; Guidelines.

Disclosure of Interests

The authors have no conflicts of interest to disclose.

Contribution to Authorship

MH and CL wrote the manuscript together with VS. VS also provided a critical review and text editing. MDT was the project administrator, conceived the idea and provided validation and visualization of the final manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

1. Huri, M, Seravalli, V, Lippi, C, Tofani, L, Galli, A, Petraglia, F, Di Tommaso M. Intrahepatic cholestasis of pregnancy – Time to redefine the reference range of total serum bile acids: A cross-sectional study. BJOG. 2022; 00: 1– 10.
2. Smith DD, Kiefer MK, Lee AJ, Davis SB, Summerfield TL, Landon MB, Rood KM. Effect of Fasting on Total Bile Acid Levels in Pregnancy. Obstet Gynecol. 2020 Dec;136(6):1204-1210.
3. Adams A, Jacobs K, Vogel RI, Lupo V. Bile acid determination after standardized glucose load in pregnant women. Am J Perinatol Reports. 2015; 05: e168–e171.
4. Ovadia C, Seed PT, Sklavounos A, Geenes V, Di Ilio C, Chambers J, et al. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of aggregate and individual patient data meta-analyses. Lancet. 2019 Mar 2;393(10174):899-909.
5. Walker IA, Nelson-Piercy C, Williamson C. Role of bile acid measurement in pregnancy. Ann Clin Biochem. 2002 Mar;39(Pt 2):105-13.
6. Smith DD, Rood KM. Intrahepatic Cholestasis of Pregnancy. Clin Obstet Gynecol. 2020 Mar;63(1):134-151.