Reconsidering absolute diagnostic thresholds in intrahepatic cholestasis of pregnancy

OBJECTIVE: Intrahepatic cholestasis of pregnancy (ICP) is characterized by pruritus and elevated serum bile acid levels after 20 weeks’ gestation, and it is associated with adverse perinatal outcomes such as fetal demise, preterm birth, and neonatal respiratory distress syndrome. Determining total bile acid levels is critical for ICP diagnosis and management, and current guidelines use an absolute threshold of 10 \( \mu \text{mol/L} \) for diagnosis and thresholds of 40 and 100 \( \mu \text{mol/L} \) for disease severity.\(^1\) However, the normal reference range for total bile acid level varies depending on assay methodology,\(^2\) limiting the utility of absolute diagnostic thresholds in diagnosing and treating ICP. We sought to evaluate variation in total bile acid assays by laboratory, testing method, and fasting state.

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Bile acid test name</th>
<th>Reference range (( \mu \text{mol/L} ))</th>
<th>Population used for reference range(^a)</th>
<th>Method of quantitation(^b)</th>
<th>Fasting requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quest</td>
<td>Bile acids, pregnancy</td>
<td>( \leq 8.3 )</td>
<td>Not available</td>
<td>Chromatography-MS</td>
<td>Overnight fasting preferred</td>
</tr>
<tr>
<td>Quest: Chantilly</td>
<td>Bile acids, total</td>
<td>( \leq 19 )</td>
<td>Not available</td>
<td>Spectrophotometry (enzymatic)</td>
<td>Fasting for 8 h</td>
</tr>
<tr>
<td>Quest: San Juan Capistrano</td>
<td>Bile acids, fractionated and total</td>
<td>( \leq 6.8 )</td>
<td>Not available</td>
<td>Chromatography-MS</td>
<td>Overnight fasting preferred</td>
</tr>
<tr>
<td>Labcorp</td>
<td>Bile acids</td>
<td>( \leq 10.0 )</td>
<td>Not available</td>
<td>Enzymatic</td>
<td>Fasting preferred, but for women who need peak bile acid testing, samples may be taken postprandially</td>
</tr>
<tr>
<td>Labcorp</td>
<td>Bile acids, fractionated and total</td>
<td>( \leq 9.2 )</td>
<td>Not available</td>
<td>HPLC-MS-MS</td>
<td>Fasting</td>
</tr>
<tr>
<td>ARUP</td>
<td>Bile acids, total</td>
<td>( \leq 10 )</td>
<td>120 healthy men and women after fasting overnight(^b)</td>
<td>Quantitative enzymatic</td>
<td>Fasting for 8 h</td>
</tr>
<tr>
<td>ARUP</td>
<td>Bile acids, fractionated and total</td>
<td>( \leq 7.0 )</td>
<td>120 healthy men and women after fasting overnight(^b)</td>
<td>HPLC-MS-MS</td>
<td>Fasting for 8 h</td>
</tr>
<tr>
<td>Northwell Health Labs(^c) (Mayo Clinic)</td>
<td>Bile acids, fractionated and total</td>
<td>( \leq 9.0 )</td>
<td>Not available</td>
<td>HPLC-MS-MS</td>
<td>Fasting</td>
</tr>
<tr>
<td>Dynacare (Canada)</td>
<td>Bile acids, total</td>
<td>( \leq 10.0 )</td>
<td>Not available</td>
<td>Not available</td>
<td>Fasting specimen preferred</td>
</tr>
<tr>
<td>Exeter (United Kingdom)</td>
<td>Bile acids</td>
<td>( \leq 10.0 )</td>
<td>Not available</td>
<td>Not available</td>
<td>Last trimester, no mention of fasting</td>
</tr>
<tr>
<td>Sonic (Australia)</td>
<td>Total bile acids</td>
<td>( \leq 10.0 )</td>
<td>Males and females after unspecified fasting period, age not defined</td>
<td>Quantitative enzymatic</td>
<td>Fasting for 8 h</td>
</tr>
</tbody>
</table>


HPLC-MS-MS, high-performance liquid chromatography—tandem mass spectrometry; MS, mass spectrometry.

\(^a\) Data obtained by accessing the laboratory website or through direct phone calls to company representatives. Data that could not be obtained by either method were listed as “not available”.

\(^b\) Pregnant women excluded; age range not defined; \(^c\) Testing via Labcorp Esoterix.

STUDY DESIGN: We compiled a list of laboratories offering total bile acid measurement within North America, the United Kingdom, and Australia. Bile acid test type, reference range, and fasting requirements were obtained via laboratory websites or by phone. Reference ranges were compared with ICP diagnostic (10 μmol/L) and severity thresholds (40 or 100 μmol/L).

RESULTS: We identified 7 laboratories with total bile acid assays located in the United States (4), Canada (1), United Kingdom (1), and Australia (1) (Table). Four laboratories also offered a fractionated assay (ARUP, Salt Lake City, Utah; Labcorp, Dublin, Ohio; Quest Diagnostics, San Juan Capistrano, California; and Northwell, Calabasas Hills, California). Depending on the test used, the upper limit of normal for total bile acids ranged from 6.8 to 19.0 μmol/L, with lower thresholds for fractioned assays (6.8–9.2 μmol/L) than for unfractionated assays (10–19 μmol/L). Only 1 laboratory provided a pregnancy-specific range (<8.3 μmol/L; Quest). Bile acids were measured using high-performance liquid chromatography, gas chromatography with mass spectrometry, or through quantitative enzymatic methods using spectrophotometry. Fasting was preferred or required in 10 of 11 assays, either overnight (n=2), for 8 hours (n=4), or for an unspecified duration (n=4). Using ICP severity thresholds, total bile acid levels >40 μmol/L or ≥100 μmol/L were 2 to 6 or 5 to 15 times the upper limit of normal, respectively, depending on the assay used.

CONCLUSION: Multiple bile acid assays are available, but the normal reference range varies according to assay methodology and fasting requirements. This leads to challenges in clinical management of ICP because absolute bile acid levels are not equivalent between assays when different techniques are used. For example, a study on fasting bile acid values in ICP used an enzymatic assay with a normal reference range of 0 to 19 μmol/L, but ICP was defined by a level >10 μmol/L. Meta-analyses on ICP have also compared absolute bile acid levels across various studies regardless of measurement technique. It would be beneficial to standardize the measurement of total bile acids in pregnancy if absolute bile acid levels (ie, 10, 40, or 100 μmol/L) are to be used to diagnose ICP or define its severity. Until such standardization is established, obstetrical care providers should interpret bile acid values on the basis of the assay used, understanding that results obtained through different techniques are not equivalent, and that assessment under fasting conditions often produces lower bile acid levels than postprandial assessment.

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The authors report no conflict of interest.

REFERENCES