

# Is it time to change the diagnostic thresholds for Intrahepatic Cholestasis of pregnancy?

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**Objective.** To establish pregnancy-specific reference intervals for fasting and postprandial total serum bile acids (TSBA) levels.

**Materials and Methods.** A prospective cohort study of TSBA levels in healthy pregnant women. Both fasting and postprandial TSBA levels were measured in 612 women over one year (528 fasting and 377 postprandial samples). Exclusion criteria were an established diagnosis of intrahepatic cholestasis of pregnancy (ICP) or any co-existing condition of increased risk for ICP.

**Results.** Reference ranges were established of 4.4-14.1 μmol/L for fasting TSBA (median 7.6 μmol/L), and 4.7-20.2 μmol/L for postprandial TSBA levels (median 9.1 μmol/L). The postprandial were significantly higher than the fasting measurements, with a median increase of 1.0 μmol/L. A correlation was found between fasting and postprandial concentrations, as well as with fetal gender, parity, and the use of assisted reproductive technologies. A seasonal pattern was noticed for both fasting and postprandial levels, with the highest values in the winter season (p < 0.01 and 0.02, respectively).

Maternal characteristics and reference interval calculations of TSBA (fasting and postprandial)

Age (years)	34 (30, 38)	N 612
BMI (kg/m <sup>2</sup> )	22.71 (20.6, 25.6)	N 610
Gestational weight gain (kg)	12 (9, 15)	N 602
Neonatal weight (g)	3268.9 (± 466.47)	N 611
Reference fasting TSBA (μmol/L)	7.6 (6.4, 9.1)	N 528
Lower limit (95% CI)*	4.4 (4.2-4.7)	
Upper limit (95% CI)*	14.1 (12.7-15.5)	
Reference postprandial TSBA (μmol/L)	9.1 (7.1-11)	N 377
Lower limit (95% CI)*	4.7 (4.5-5.3)	
Upper limit (95% CI)*	20.2 (17.3-32.3)	

\*Reference intervals were calculated using nonparametric method to account for non-normally distributed results. The lower (2.5th) and upper (97.5th) reference limits are noted with 95% confidence intervals (CI) indicated in brackets.  
 \*\*Data are expressed as mean ± SD or median (I\*, 3<sup>o</sup> IQR) based on their distribution

**Conclusions.** Normal pregnancy is a sub-cholestatic state and is associated with a physiological elevation of TSBA levels compared to non-pregnant adults, therefore a higher threshold should be considered for the diagnosis of ICP. It is suggested that the upper reference limit observed in our healthy pregnant population should be used: fasting TSBA values ≥ 14 μmol/L and postprandial TSBA values ≥ 20 μmol/L. Since the fasting TSBA value is more specific for the diagnosis, while the postprandial is important for severity assessment, we recommend measuring both, rather than obtain a random sample.