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Intrahepatic Cholestasis of Pregnancy: The Usefulness of Serum Bile Acid Profile for Diagnosis and Treatment

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1. Introduction

Intrahepatitic cholestasis of pregnancy (ICP), also called obstetric cholestasis, is a specific liver disease that takes place in the second or third trimester of gestation and spontaneously disappears after delivery (Shaw et al., 1982; Brites et al., 1998). Firstly reported by Ahfiled in 1883, it was after 1950 that the disease began to be considered of significance when several clinical cases were studied. It has lastly been highlighted the association of ICP with perinatal mortality and morbidity of newborns from cholestatic mothers (Pradhan, 2002). For pregnant women with cholestasis, quality of life can be impaired by itching, jaundice and fat malabsorption, but the prognosis of the mother is good. However, ICP is a condition with possible lethal outcome if it is not handled with care. Therefore, an early and accurate diagnosis of a risky pregnancy produced by ICP together with a safe medical treatment are essential to improve fetal outcome. (Diaferia et al., 1996; Bacq et al., 1995; Meng et al., 1997; Milkiewicz et al. 2002).

Puritus is usually the chief complaint and generally starts in the palms and soles, progressing to the arms and legs and eventually involves the trunk and face. There is additional progression from occasional to constant pruritus which can lead to sleep deprivation and irritability. Jaundice occurs in approximately 17-75% of ICP cases and telangiectasia and palmar erythema may be present in up to 60% of clinical cases (Mullaly et al.2001). It was found a weak correlation between bile acid levels and pruritus suggesting that the subjective symptom cannot be taken to predict severity of the disease. (Glantz et al., 2004)

Although it is an interesting matter, severity of maternal signs and symptoms does not seem to correlate with fetal prognosis and many obstetric clinics still choose to manage ICP pregnancies with expectance. Maternal monitoring of fetal movement has been described as normal until a few hours before delivery in cases of subsequent fetal demise.

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The prevalence of pregnancy cholestasis varies throughout the word being South America, specially Chile, the geographical area of higher percentage (12-22%) (Pradhan, 2002).

The exact pathogenesis of ICP is still unknown being probably of multifactorial causes. Genetic studies revealed a positive family history in 33-50 %, the condition is known to repeat in 40-70% of pregnancies and it is reported an endemic occurrence showing that a genetic factor should be taken into account (Lammert et al., 2000).

Levels of estrogens could also be involved in the development of ICP. This theory is based on the observations that the most common date of presentation of ICP is the third trimester of pregnancy when the estrogen levels are highest and is resolved promptly after delivery when placental hormones return to their normal levels. On the other hand, obstetric cholestasis resembles a similar condition that some women develop while taking oral contraceptive pills containing estrogens in the formulation. Moreover, twin pregnancies bothly display a higher incidence of ICP and more pronounced rises in estrogen levels (Pradham, 2002; Lammert et al., 2000).

In the pathogenesis of ICP, progesterone and its metabolites seem to play an even more important role than estrogens. It is described in the literature the development of ICP related symptoms after the administration of progesterone in a woman with a history of ICP (Lutz et al., 1969; Mullaly et al., 2001). It was also demonstrated that the profile of progesterone metabolites in plasma from patients with ICP is markedly different from the profile observed in normal pregnants (Sjövall et al, 1970, Laatikainen et a. 1974; Pascual et al. 2002).

Though the pathogenesis of the fetal death in ICP is not fully understood, the action of bile acids is strongly suspected to be implicated in mortality. During ICP there are a high bile acid levels in ammiotic fluid, cord plasma and meconium increasing the flux of bile acids from mother to fetus (Lammert et al., 2000). In cases of intrauterine fetal loss, observation of fetus autopsy is consistent with death from acute intrauterine anoxia. Meconium and bile acids, especially cholic acid (CA), have been indicated to induce vasoconstriction of human placental chorionic veins in vitro (Serrano et al., 1998) as well as to cause acute umbilical vein constriction (Altshuler et al., 1989; Altshuler et al., 1992). Although bile acid mechanisms are not yet defined, it is well known their toxic action. Thus, there is some experimental evidence that bile acids are involved in the mechanisms triggering fetal asphyxia in pregnancies complicated with ICP (Brites, 2002). It was also demonstrated that taurocholic acid (TCA), a bile acid increased in ICP, causes a decrease in the rate of contraction of rat cardiomyocytes and loss of synchronous beating (Williamson et al., 2001). Secondary bile acids, lithocholic acid (LCA) and deoxicholic acid (DCA) which are also elevated in patients with ICP, are able to cross the placenta (Heikkinen et al., 1980). These compounds have been shown to be fetotoxic in experimental animals causing embrio death, birth deformities and fetal growth restriction (Zimber et al., 1990).

In vitro studies indicate that myometrial cell preparations from ICP women show a more intense response to oxytocin stimuli than do cells from healthy women (Israel et al., 1986) and an increase of oxytocin-receptor expression after being incubated with CA (Germain et al., 2003). These findings could be related with preterm delivery in ICP although the exact mechanism of action is still unclear for a complete explanation.

2. Diagnosis and treatment

Usually, diagnosis of ICP is based on pruritus with mild or moderate elevated levels of amino transferases and raised total serum bile acids (TSBA) (Reyes et al., 1993). However, it is often difficult to accomplish an accurate diagnosis by performing solely routine laboratory tests because they are also altered in some other conditions of pregnancy. In fact, the existence of subclinical cholestasis during pregnancy may also make difficult the diagnosis of the disease. Moreover, pruritus in pregnancy is a common symptom in ICP but this evidence is not sufficient to discriminate women with ICP from those with benign condition of pruritus gravidarum (Meng et al., 1997, Castaño et al., 2006).

A number of other disorders may erroneously be interpreted as ICP during pregnancy: skin diseases, specific dermatoses of pregnancy, allergic reactions, renal pruritus and hematological disorders such as Hodkin´s disease and polycythemia rubra vera (Pusl et al., 2007). The most sensitive indicator in the diagnosis of ICP is a rise of serum bile acid levels. Total serum bile acids in healthy pregnancies are slightly higher in pregnant (6.6 ± 0.8 μM) than in non-pregnant women (3.2 ±0.7 μM) (Castaño et al., 2006) but levels up to 11.0 μM are accepted as normal in late gestation (Brites et al., 2002). Higher fetal complication rates have been associated with TSBA levels higher than 40 μM (Glanz et al., 2004, Pusl et al., 2007). Spontaneous preterm deliveries, asphyxia events and meconium staining of amniotic fluid, placenta and membranes increased by 1-2% for each additional μmol/L of total bile acid concentrations. However, these events did not increase until bile acid levels exceeded 40 μM (Glanz et al., 2004). It is suggested that patients could be expectantly managed when TSBA levels remain below 40 μM and when pregnant women refer pruritus it should be surveilled with the aid of repeated determinations of serum bile acids.(Glantz et al., 2004)

Recently, a subgroup of asymptomatic pregnant women with high levels of TSBA, and normal liver function tests but not showing pruritus has been classified as asymptomatic hypercholanaemic pregnants (AHP) (Castaño et al, 2006; Lunzer et al., 1986; Pascual et al., 2002; Tripodi et al., 2003). Women with AHP did not differ from normocholanemic women respect to clinical, biochemical or perinatal characteristics. AHP does not appear to be a clinical entity by itself, but a subgroup of normal pregnancies with higher levels of TSBA specially the conjugated dihydroxy serum bile acids (Castaño et al., 2006).

It has been reported that TSBA levels observed in ICP overlapped with those of healthy and AHP pregnant women, making it difficult to obtain a differential diagnosis on the basis of TSBA measurements as the key for recognition of the disease (Castaño et al., 2006, Muresan et al., 2007). Indeed, ICP may be present without elevated bile acids (Muresan et al., 2007; Egerman et al., 2004). It has also been reported that up to 45 % of patients with clinical diagnosis of ICP may have normal fasting serum bile acids (Mullaly et al., 2001).

Therefore a clear question emerges from these observations: the monitoring of the patient should be discontinued if the TSBA levels are within the reference values? What happen if these levels change over the course of the week of delivery?

With regard to this point, serum bile acid profile has proved to be more informative than the determination of TSBA (Baqc et al.; 1995, Meng et al., 1997; Castaño et al., 2006; Lucangioli et al., 2009). Although many authors agree on the benefits of evaluating serum bile acids individually, there is no consensus in assigning a particular bile acid determination as the

most useful indication in order to diagnose ICP or in establishing adequate bile acids ratios to solve how to recognize the disease. One of the reasons of these differences could be attributed to different analytical methods reported with the purpose of evaluating the bile acid profiles or it could be due to ethnic differences that lead to different bile acid prevalences.

It is important to emphasize that the serum bile acid profile is useful not only to diagnose ICP but also to analyze the evolution of the disease after treatment (Castaño et al., 2006).

The pharmacological treatment of ICP with antihistamine, anion exchange resins and phenobarbital to remove peripheral pruritogens has not received wide acceptance because of their incomplete efficacy or side effects of therapy (Lammert et al., 2000). Cholestyramine is an anion exchange bile acid-binding resin giving some successful results in managing pruritus. However, this drug contributes to fat-soluble vitamin deficiency leading to postpartum hemorrhage, it does not correct liver enzyme abnormalities and it does not improve fetal prognosis in ICP (Mullally et al., 2001). Ursodeoxycholic acid (UDCA), a naturally hydrophilic bile acid is presently considered in the treatment of ICP because it improves clinical and biochemical parameters in pregnant women. The mechanisms of action of UDCA are still under discussion, but there are some evidences of protective and antioxioxidant effects of this bile acid (Lee et al., 1997; Brites, 2002; Copaci et al., 2005). It is also known that UDCA therapy alters the hydrophilicity and, therefore, the overall distribution of bile acids in the bile acid pool decreasing levels of hydrophobic and toxic bile acids as LCA (Lucangioli et al., 2009, Mullally et al., 2001). Moreover, it is known that UDCA reverse the impairment in the functionality of bile acid transport across the trophoblast, so its administration can be a valuable contribution to the fetal well-being (Serrano et al., 1998). On the other hand, UDCA has been shown to improve impaired hepatocellular secretion by mainly posttranscriptional stimulations of canalicular transporter proteins leading to enhance the elimination of bile acid metabolites and other organic anions as well as mono- and disulphate steroids (Pusl et al., 2007). UDCA seems to be well tolerated by pregnant women and no adverse effect in mothers or newborns has been observed.

3. Bile Acids: Chemical structure and functions

Bile acids (BA) are steroid compounds pertaining to hydroxyl-derivatives of 5β-cholan-24-oic acid. They have different physico-chemical properties according to the number, position and orientation of their hydroxylgroups, and by conjugation with glycine and taurine, glyco-and tauro-derivatives are produced to the liver (Lucangioli et al., 2001). Figure 1 presents the chemical structures of bile acids showing primary BA like cholic acid (CA) and chenodeoxycholic acid (CDCA) and secondary BA, deoxycholic acid (DCA), lithocholic acid (LCA) and ursodeoxycholic (UDCA) (Tripodi et al., 2003). Moreover, BA are acidic molecules with pka values of 1.5 for taurine derivatives, 4.5 for glycine derivatives and 6 for unconjugated BA.

The biological functions of BA are principally associated with lipid digestion and absorption, solubilization of cholesterol and bile formation (Roda et al., 1995). Under physiological conditions, serum BA concentrations are normally present at micromolar level in the peripheral circulation. However, in hepatobiliary and intestinal diseases, the hepatic synthesis and clearance of BA and their intestinal absorption are disturbed, enabling quantitative and qualitative changes in the pattern of serum BA (Burkard et al., 2005).

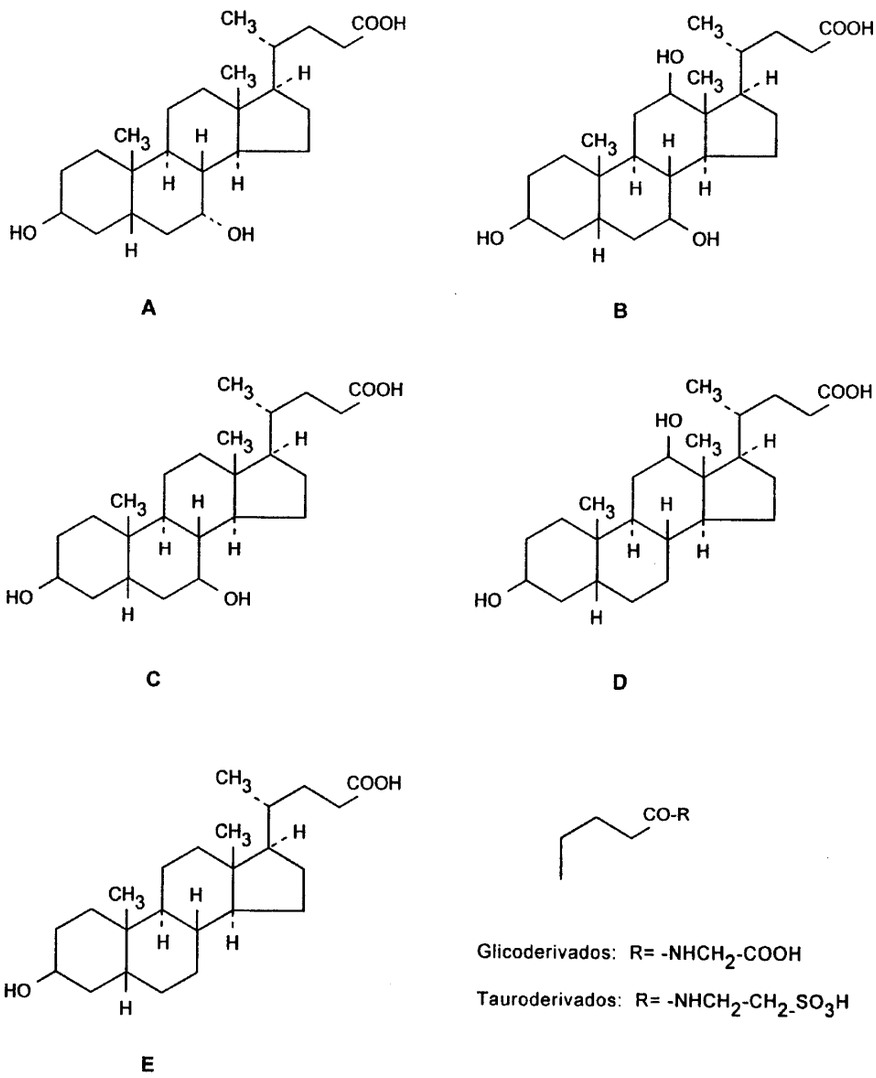


Fig. 1. Chemical structures of bile acids as free forms and their glyco-and tauroderivatives (A) UDCA, (B) CA, (C) CDCA, (D) DCA and (E) LCA

Regarding liver therapy, some BA, like UDCA and CDCA, are administered as therapeutic agents in the treatment of cholesterol gallstones. UDCA has also been used in the therapy of cholestatic liver disease (Konikoff, 2003; Paumgartner et al., 2004).

4. An overview of different analytical techniques in serum bile acid studies

4.1 Separative techniques

The analysis of BA is challenging since they are present at micromolar concentrations in biological fluids, and each BA has small structural differences between the others. Different analytical methods have been developed for the quantitation of BA in various matrices applying separative techniques. In this sense, high-performance liquid chromatography (HPLC) has been a popular technique applied in the individual analysis of BA in biological

fluids. The HPLC- methods reported involve two chromatographic systems to determine the complete BA profile, one for free BA and the other system for BA derivatives (Vescina et al., 1993). Unfortunately, the combination of HPLC with UV-detection, limited the sensitivity of the analysis due to the fact that BA have little chromophorore groups in their molecules (Fig. 1). To improve sensitivity, some derivatization methods have been described by Burkard (Gatti et al., 1997). However, these methods are time consuming. In contrast, HPLC coupled to mass (MS) detector, represents a sensitive and selective chromatographic technique to determine BA in biological matrices. Several MS techniques by ionization have been used for BA analysis like HPLC-MS and HPLC-MS/MS, though specially applied to the analysis of BA derivatives (Bootsma et al., 1999; Tagliacozzi et al., 2003), being the electrospray ionization (ESI) the best detection system. In contrast, unconjugated BA are not detectable by MS/MS due to the lack of any specific fragment ions originated from their molecules. However, Burkard et al. have developed an HPLC-MS/MS method to quantify free and derivatives UDCA, CDCA and DCA in serum. Quantification of unconjugated BA was performed using single ion monitoring mode of the deprotonated molecules (Burkard et al., 2005).

Gas chromatography (GC), has also been applied to the analysis of BA in biological fluids (Batta et al., 1999), in some cases, coupling MS as detector (Niwa, 1995; Setchell,et al., 1983). However, GC-MS methods are not simple as they require an extensive sample pre-treatment like extraction, purification and hydrolysis of conjugated BA and the preparation of volatile derivatives prior to detection of all the products (Perwaiz et al., 2010).

Thin layer chromatography (TLC) is other separative technique applied to the quantitation of BA in biological matrix. This technique has used to determine conjugated and unconjugated BA, however, UDCA and CDCA cannot be resolved. Brites et al. applied TLC in combination with HPLC-UV and GC-MS to quantitate BA in different biological sample (Rodriguez et al., 1999). However, TLC is not widely extended in laboratories

4.1.1 Capillary electrophoresis

Capillary electrophoresis (CE) is a family of related techniques that employs narrow-bore capillaries to perform high efficiency separations of both large and small molecules, favoured by the use of high voltages, which may generate electroosmotic and electrophoretic flows of buffer solutions and ionic species, respectively, within the capillary.

The CE advantages with respect to other analytical techniques, such as very high resolution in short time of analysis, versatility, the possibility to analyze molecules without chromophore groups, simultaneous analysis of various compounds with different hydrophobic characteristics, small volume of sample, and low cost, have made this technique adequate for the analysis of numerous types of compounds like biological macromolecules, chiral compounds, inorganic ions, organic acids, DNA fragments and even whole cells and virus particles. An increasing number of applications of CE are in progress in many clinical laboratories. Significant potential benefits in the future will impact on clinical diagnosis and therapy. Specially, there are several instances in which the limited availability of biological fluids significantly preclude the analysis of various relevant

biochemical compounds that can be achieved because small volumes of sample are required by this technique.

Over the last 20 years, capillary electrophoresis has evolved into a powerful analysis technique with different applications. Firstly created to be focused on water-soluble ionic analysis, CE has grown to a very high degree of development and now it is employed in a wide variety of pharmaceutical, biopharmaceutical and clinical applications. Its development in today´s world is in the step of miniaturization processes in science and technology including analytical chemistry.

Medical diagnosis and quality control assays are areas that are specially benefited from miniaturization. The ability to quantify each time smaller amounts of compounds in biological fluids together with the capacity of analytical systems to handle low nanoliter sample volumes extremely improve the diagnosis of many diseases.

The main disadvantage in the analysis of biological samples are the following: a) small amounts of biological fluids or tissues available, that usually are not enough to determine their components by traditional techniques; b) small quantities of these components that, in some cases, are present in trace amounts; c) presence of numerous interferences and d) requirement of simultaneous separation and determination of more than one component. These are the major reasons for calling this type of sample as a "complex matrix".

In clinical applications, the analytical system should be capable of handling nanoliter volumes of sample, effective enough to determine analytes at subnanomolar concentrations, and should provide high selectivity and successful separations of different molecules in a single run.

Capillary electrophoresis seems to possess many of the advantages required for a nanotechnique employed with clinical purpose.

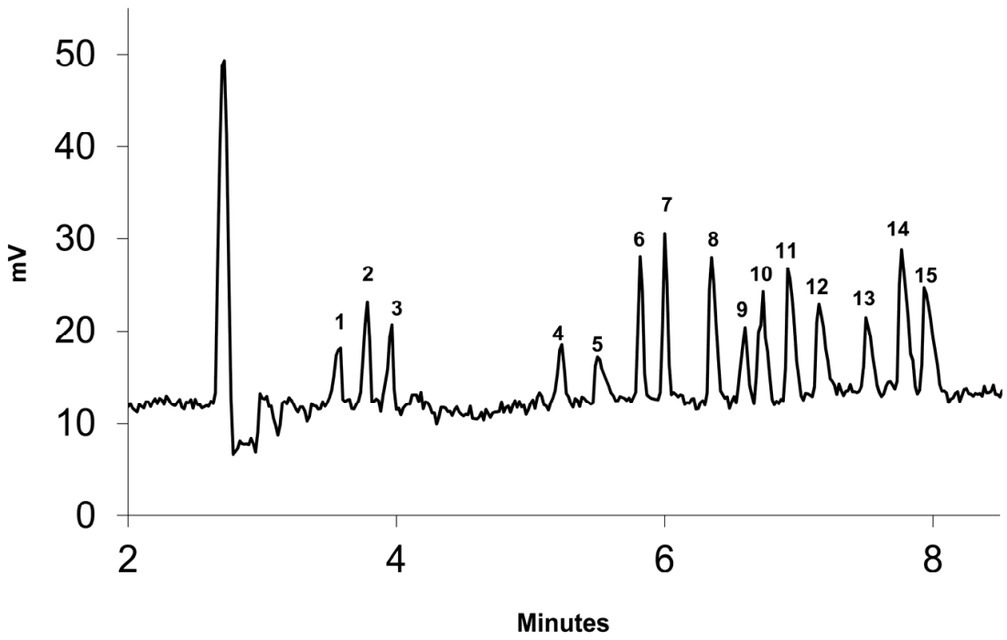
A CE system has been developed for the analysis of BA profile in plasma. The CE system is based on a micellar electrokinetic chromatography, as a mode of CE, with the use of sodium dodecyl sulfate as micellar agent and cyclodextrins (CD-MEKC) (Tripodi et al., 2003) using UV detection. The CD-MEKC system allowed the simultaneous and complete resolution of 15 BA (taurine, glycine and unconjugted BA) in serum sample in less than 12 min with good precision and accuracy using a simple sample preparation (Fig. 2).

4.2 Enzymatic assay

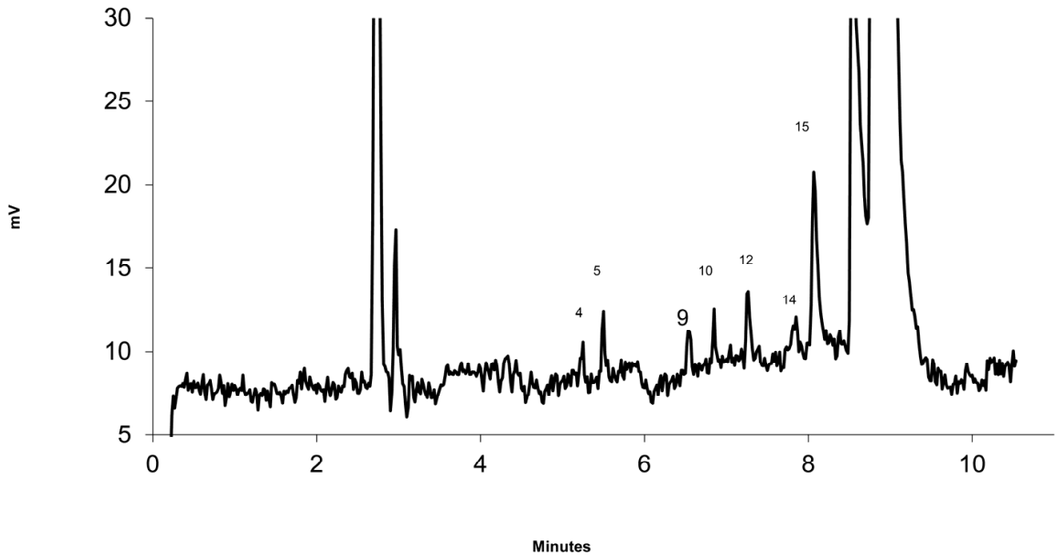
Enzymatic methods have been used to determine total BA in biological matrices. A NAD-dependent steroid dehydrogenase, oxidizes hydroxycholanoates with formation of NADH, which is measured by UV or fluorimetric methods (Griffiths et al., 2010). 3∞-hydroxysteroid dedydrogenase is used in clinical chemistry for analysis of plasma BA to monitor changes in liver diseases, however, only BA with 3∞- hydroxysteroid in its molecule can be determined.

4.3 Immunoassays

Many radioimmunoassay and enzyme immunoassays methods have been applied for simple and rapid analysis of common total BA in plasma. An important disadvantage of these methods is specificity, particularly at low concentrations of BA (Griffiths et al., 2010).



A): Electropherogram of a serum sample matrix spiked with 15 bile acid standards, 6-10µM for free bile acids and 4-6µM for conjugated bile acids. 1: UDCA, 2: GUDCA, 3: TUDCA, 4: LCA, 5: CDCA, 6: GLCA, 7: TLCA, 8: GCDCA, 9: CA, 10: TCDCA, 11: DCA, 12: GCA, 13: TCA, 14: GDCA, 15: TDCA



B): Electropherogram of a serum sample from an ICP patient. 4: LCA, 5: GLCA, 9: CA, 10: TCDCA, 12: GCA, 14: GDCA, 15: TDCA

Fig. 2. Electropherograms of serum bile acid assessed by capillary electrophoresis

5. Clinical interpretation of serum bile acid profile

Although physicians have so far used TSBA levels in the diagnosis of ICP, there is sufficient evidence that they are not efficient enough as it would be expected. A single value of TSBA could be replaced by assessing the profile of bile acids or certain ratios calculated between certain BA in particular. It is therefore a priority for physicians to take into account these results and interpret correctly the laboratory data for a better evaluation and control of the ICP disease. However, not all researchers agree on which bile acid provides more information, possibly because of methodological differences in addition to ethnic characteristics that might have influence on serum bile acid profiles from different populations of the world.

Laatikaimen et al. in 1978 and many other authors later (Laatikaimen et al., 1978, Brites et al., 1998, Bacq et al., 1995) showed a marked predominance of CA in ICP while Castaño et al (2006) demonstrated the presence of LCA as the preponderant bile acid in this disorder. Brites et al. in 1998 showed that elevations of glycocholic acid provide a sensitive biochemical test for the diagnosis of ICP with 95 % efficiency but state that TCA is even better having 100% efficiency (Brites et al., 1998). There are several reports which have demonstrated that different ratios calculated from individual bile acid determinations are useful in the comprehension of different types of liver diseases (Brites et al., 1998, Azer et al., 1997, Pusl et al., 2007). Heikkinen in 1983 and later Brites in 1998 (Heikkinen, 1983; Brites et al., 1998) demonstrated that the CA/CDCA ratio is increased in ICP approximately from 4:1 to 8:1 respect to normal pregnancies.

Brites et al (1998) employed HPLC for conjugated bile acids analysis and TLC for free bile acids, highlighting that free UDCA was not quantified because it did not separate from CDCA during TLC separation. On the basis of this methodology the authors established that better criterium to diagnose ICP is TSBA >11μM, CA/CDCA >1.5, %CA>42%, Glycine/Taurine <1 and GCA/TCA>2.

However, a latter report has recently determined that CA / CDCA ratio contribute little to the diagnosis of ICP (Huang et al., 2009). Using capillary electrophoresis as analytical technique, it has been demonstrated not only that CA/ CDCA ratio was below the unit but also a shift towards a hydrophobic composition with higher levels of LCA and free bile acids was found in women with ICP concluding that LCA is a useful parameter in the differential diagnosis of ICP and AHP (Castaño et al., 2006).

With regard to the analysis of serum bile acids it was found that AHP women showed TSBA levels above the usually accepted cut-off values and their serum bile acid profiles demonstrated that UDCA levels were higher in AHP patients compared to normal pregnant women and to all ICP patients before treatment, with either low or high score pruritus (table 1). Moreover, in AHP patients LCA levels showed no difference with values of normal pregnant women (Castaño et al., 2006). An inspection of the UDCA /LCA ratio, the highest value was observed in AHP patients because of the increment of UDCA levels observed in these patients. It could be possible to hypothesize that this high ratio has a protective effect in AHP patients since they do not develop ICP even with elevated TSBA and it is possible that UDCA/LCA ratio could have a higher discrimination power than individual bile acid determinations. These evidences should be demonstrated in further studies.

	Non-pregnant women (n=10)	Normocholamenic (n=18)	AHP (n=12)	ICP (n=41)
Total SBA (μM)	3.2 ± 0.7	6.6 ± 0.8	21.9 ± 3.2	29.5 ± 3.3
LCA (μM)	0.05 ± 0.06	0.3 ± 0.2	0.10 ± 0.03	8.2 ± 1.7
CDCA (μM)	0.9 ± 0.4	0.7 ± 0.3	3.3 ± 2.1	4.2 ± 0.9
DCA (μM)	0.2 ± 0.1	1.3 ± 0.7	4.0 ± 1.2	4.9 ± 1.1
CA (μM)	0.7 ± 0.4	0.7 ± 0.1	1.1 ± 0.7	3.6 ± 0.8
UDCA (μM)	0.9 ± 0.3	4.5 ± 0.9	13.3 ± 1.9	8.5 ± 1.6
Free/conjugated	1.1 ± 0.3	0.05 ± 0.02	0.3 ± 0.1	1.3 ± 0.3
Taurine/Glycine	5.0 ± 0.2	5.6 ± 0.2	6.7 ± 0.2	5.7 ± 0.1

Table 1. Comparison of TSBA levels and SBA profiles in different groups studied. Results are expressed as means ± SEM. Bile acids are expressed in their free, glycine and taurine forms. From reference Castaño 2006.

Later, the same authors (Lucangioli et al., 2009) proposed LCA as an alternative biomarker and a more sensitive parameter to evaluate effectiveness of UDCA treatment. It was observed a relief of pruritus together with a dramatic decrease in LCA concentrations in all patients following UDCA therapy (Fig 3). It was also found that TSBA concentrations overlapped before and after UDCA therapy (Fig. 4). Instead, LCA concentrations were high in all ICP patients but decreased only in the group of treated patients. Thus, the mentioned results indicated that LCA is a more sensitive marker than TSBA to evaluate the therapeutic monitoring of ICP. In the same work the authors observed that a decrease in the

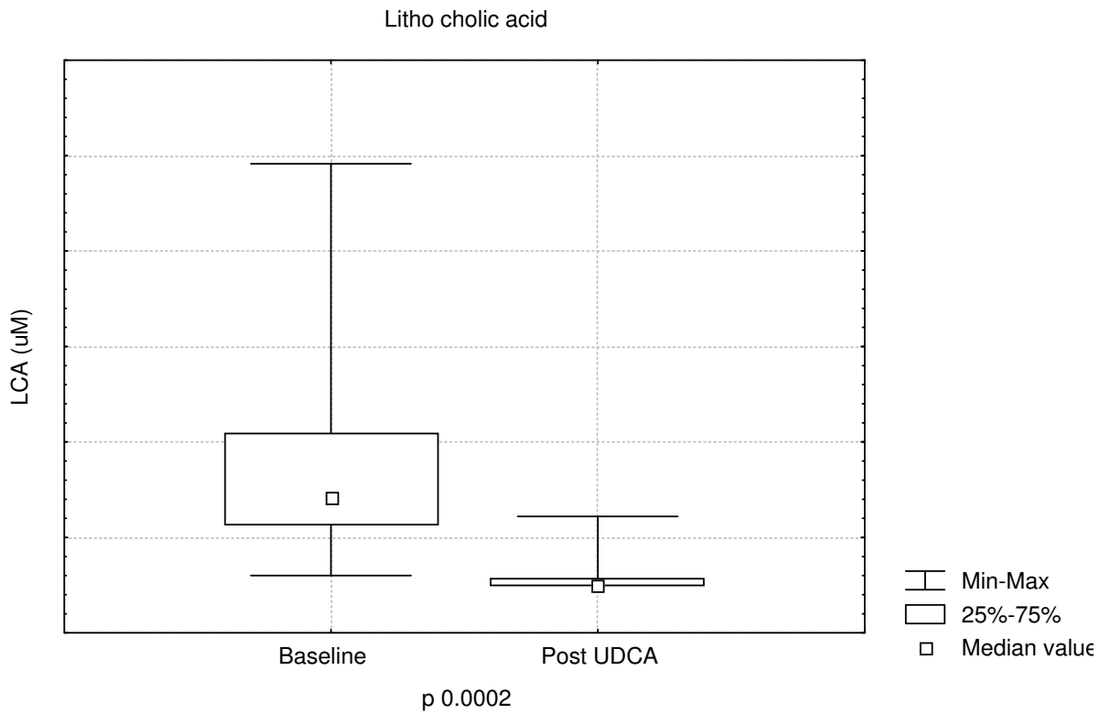


Fig. 3. The effect of UDCA therapy in LCA

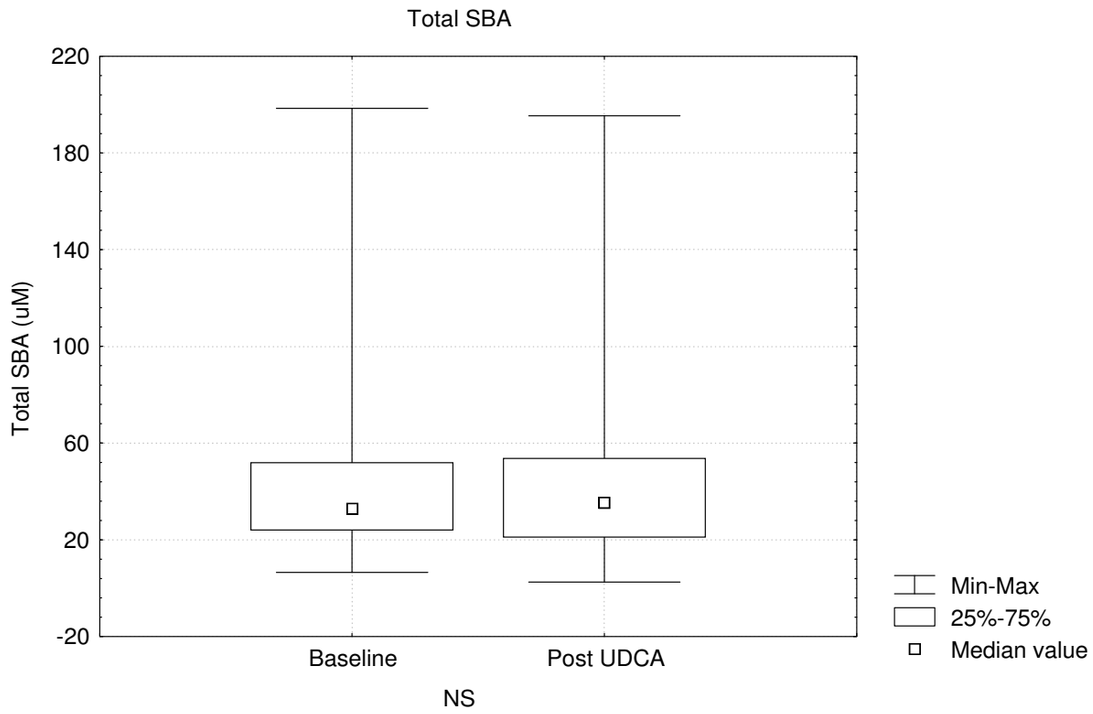


Fig. 4. The effect of UDCA therapy in TSBA

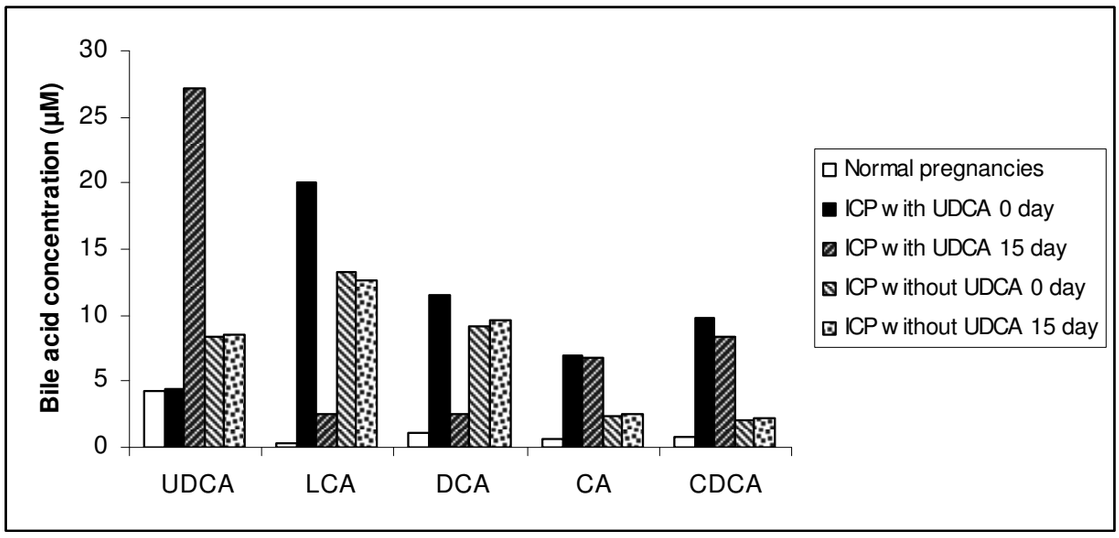


Fig. 5. Comparison of SBA profiles (mean ± SEM) in normal pregnancies (n = 20) and ICP patients with (n =23) and without (n = 5) UDCA treatment. Bile acids are expressed as the sum of their free, glycine and taurine forms. *p<0.001 (difference in LCA from day 0 to 15 with UDCA treatment), **p<0.03 (difference in DCA from day 0 to 15 with UDCA treatment)

concentrations obtained in individual SBA did not have any time effect, since SBA profiles in ICP patients without therapy did not change during 15 days (Fig 5). This result showed that the decrease in LCA and DCA concentrations could be attributed only to UDCA treatment (Lucangioli et al, 2009).

In conclusion, although there is no consensus about which bile acids are better indicators for evaluating the ICP, it must be emphasized that clinicians should gradually abandon using the value of TSBA determination to assess bile acid profile as a more accurate approach in ICP diagnosis and treatment.

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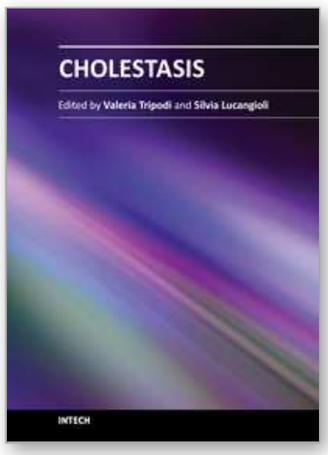
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This book covers different aspects on the understanding of mechanisms, effects, and management of cholestasis. This unique compendium contains important citations, an invaluable amount of research work, and many applications, which are outstanding resources for clinicians, pharmacists, biochemists, upper-level undergraduate, graduate, and continuing-education students who are dedicated to discovering new knowledge on cholestasis.

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