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Case Report

Biliary acids is a critical laboratory value in pregnant women: a case report as an opportunity to improve the quality of care

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ABSTRACT

Biliary acids (BA) levels were found greatly increased to 72.1 µM/l in a pregnant woman. Bambino Gesù Children's Hospital had not established critical alarm values for BA, so communication of the result was overpassed. After 30 hours, the patient referred to the emergency room of another hospital for the assessment of the pregnancy course and BA re-evaluation, which in turn resulted normal. BA levels in our sample were re-analyzed in both laboratories and high levels were confirmed. We utilized an enzymatic cycling colorimetric method measuring primary, secondary and tertiary BA. The patient was on therapy with ursodeoxycholic acid (UDCA) explaining total BA results difference reported in the two different blood samples. BA accumulation maybe leads to fetal complications or loss and a quick communication of the result to clinician could potentially be life-saving for the baby. We implemented corrective actions to avoid adverse events by the introduction of a note on the report, warning of UDCA therapy interference in BA dosage and recommending the suspension of therapy 24 hours before blood sampling; furthermore, in order to provide high level of health care, we introduced an alarm value for fertile women in our critical values list.

Keywords: BA, Laboratory critical values, Pregnancy complications, Fetal loss, Critical communications, Cholestasis

INTRODUCTION

Cholestasis of pregnancy is a potentially very dangerous condition for the fetus and elevated bile acid values should be promptly evaluated by the gynecologist.[1-3] This is an interesting case report that prompted us to undertake corrective actions to improve the quality of care and potentially life-saving actions.

CASE REPORT

A 29 years-old pregnant woman was referred to Bambino Gesù Children's Hospital for evaluation of BA levels previously found altered. Since the tenth week of pregnancy, serum BA levels were progressively increasing from 10.4 µM/l, to 12.4 µM/l at the seventeenth week, to 17.2 µM/l at the nineteenth week of pregnancy. At twenty-third weeks of pregnancy BA levels were found greatly increased to 72.1 µM/l. Because of BA levels >10 µM/l the patient was taking UDCA therapy but the information was not known at the time of sampling.

Bilirubin and liver enzymes have been always reported as normal as well glycosylated hemoglobin, blood count, vitamin D level and thyroid hormones (Table 1). The

routinary pregnancy screening for infectious disease have been reported negative. Body mass index was reported as 27.89 kg/m^2 and blood pressure was normal (100/60 mmHg).

Table 1: Laboratory tests results of the patient.

Lab test	10 weeks of pregnancy	17 weeks of pregnancy	19 weeks of pregnancy	23 weeks of pregnancy
BA (µM/l)	10.4	12.4	17.2	72.1
WBC (10^3/µl)	5.40	6.20	5.29	5.44
RBC (10^6/µl)	4.29	4.23	4.03	4.06
Hb (g/dl)	11.0	11.2	10.7	10.9
PLTs (10^3/µl)	404	384	379	301
ALT/ AST (U/l)	27/ 27	18/ 19	16/ 15	14/ 17
Bilirubin total/ direct (mg/dl)	0.35/ 0.18	*N.A.	*N.A.	*N.A.
Glucose (mg/dl)/ HbA1c (mmol/mol)	79/ 32	*N.A./ 31	*N.A.	73/ 24
BUN (mg/dl)	9	*N.A.	*N.A.	*N.A.
Creatinine (mg/dl)	0.48	*N.A.	*N.A.	*N.A.
Uric acid (mg/dl)	2.6	*N.A.	*N.A.	*N.A.
25-OH vitamin D3 (ng/ml)	20.8	35.2	*N.A.	37.5
TSH (µIU/ml)/ FT3 (pg/ml)/ FT4 (ng/dl)	1.24/ 3.29/ 1.45	1.06/ 2.48/ 1.25	*N.A.	1.47/ 2.47/ 1.23
HBsAg/ HCV Ab	Negative/ negative	*N.A.	*N.A.	*N.A.
Fibrinogen (mg/dl)	365	*N.A.	*N.A.	*N.A.
aPTT-s/aPTT-r (%)	29.9/ 1.02	*N.A.	*N.A.	*N.A.
I.N.R.	1.08	*N.A.	*N.A.	*N.A.
AT (%)	111	*N.A.	*N.A.	*N.A.
CMV IgG/IgM (U/ml)	Negative/ negative	Negative/ negative	*N.A.	Negative/ negative
Treponema pallidum total Ig	Negative	*N.A.	*N.A.	*N.A.
Measles Ab IgG/IgM (AU/ml)	Negative/ negative	*N.A.	*N.A.	*N.A.
Toxoplasma gondii Ab IgG/IgM (UI/ml)	Negative/ negative	Negative/ negative	*N.A.	Negative/ negative
Rubella Ab IgG/ IgM (UI/ml)	64.8/ negative	*N.A.	*N.A.	*N.A.
Chickenpox Ab IgG/IgM (mIU/ml)	1071.00/ negative	*N.A.	*N.A.	*N.A.

*N.A.: data not available.

Our hospital had not established critical alarm values for BA levels to communicate results to the patient or her referring doctor; clinical information, including pregnancy status, were not available at that moment, therefore the laboratory doctor reported the result overpassing communication, merely having care to make the result available to the patient in the shortest possible time.

The next day, after consulting the gynecologist, the patient referred to the emergency room of another hospital of Rome for the assessment of the pregnancy course and BA re-evaluation, which in turn resulted normal (6 µM/L).

To verify the accuracy of our result, we checked the instrument (cobas 600, Roche) and all quality controls and the assay was repeated on the same sample, confirming the previous value. We dosed our sample in the second laboratory and the high value was confirmed (65.3 µM/l).

DISCUSSION

BA are detergent molecules emulsifying fats and modulating steroids and lipid-soluble vitamins absorption. BA are also signalling molecules modulating hepatic lipids, glucose and energy metabolism and anti-bacterial agents controlling bacteria overgrowth in the gut.[4-6]

Our laboratory assay (SENTINEL Diagnostic) utilizes an enzymatic cycling colorimetric method converting BA to oxosteroids in the presence of excess NADH (nicotinamide adenine dinucleotide) and thio-NADH+ (thionicotinamide adenine dinucleotide). The enzyme 3α-hydroxysteroid dehydrogenase oxidizes primary, secondary and tertiary BA to 3α-oxosteroids. During this reversible enzymatic reaction, thio-NADH+ is concomitantly reduced to thio-NADH. The rate of production of thio-NADH, which absorbs at 404nm, is proportional to the concentration of BA present in the sample.

As quoted by the manufacturer the limit of detection of the assay is 0.19 µmol/l and measuring range is 1.0-180 µmol/l; the assay is not affected by the presence of conjugated bilirubin up to 22.4 mg/dl, unconjugated bilirubin up to 29.9 mg/dl, haemoglobin up to 1000 mg/dl, triglycerides up to 1703 mg/dl, intralipid up to 750 mg/dl, proteins up to 12.2 g/dl, sulfapyridine up to 305 mg/l, sulfalazine up to 305 mg/L and tamozolomide up to 20 mg/l.

The second laboratory utilizes a similar assay kit (Diazyme laboratories) that in the presence of Thio-NAD, the enzyme 3-α-hydroxysteroid dehydrogenase (3- α-HSD) converts bile acids to 3-keto steroids and Thio-NADH. Three-keto steroids and Thio- NADH is converted by 3-α-HSD to bile acids and Thio-NAD. The rate of formation of Thio-NADH is measured by absorbance at 405 nm. The sensitivity of the test has a linear range from 0-180 µM. According to the manufacturer, the assay precision is intra-assay precision CV% of <4% and inter-assay precision CV% of <3% and Triglycerides at 750 mg/dl, Ascorbic acid at 50 mg/dl, Bilirubin at 50 mg/dl and hemoglobin at 500 mg/dl produce less than 10% deviation.

The majority of BA pool is composed by cholic acid (CA), chenodeoxycholic acid (CDCA) and deoxycholic acid (DCA).[7] BA synthesis is tightly controlled and their levels in the circulation are always maintained low and constant.[8] BA absorption through the enterohepatic circulation is extremely effective resulting in about 95% of BA reabsorbed.[9] Most of the bile acids are conjugated to glycine or taurine and conjugation to glycine overcome taurine conjugation by 3 to 5 times.[10] Conjugated BA are secreted into bile forming mixed micelles with cholesterol and phosphatidylcholyne to prevent cholesterol precipitation and to protect epithelial cells from BA toxicity. Gut microbial bile salt hydrolase (BSH) deconjugates BA in free BA while bacterial 7α-dehydroxylase converts them to deoxycholic acid (DCA) and lithocholic acid (LCA).[11] BA can be terribly toxic if accumulated in high concentrations in tissues and different types of BA may have different effects. For example, CA enhances hepatocyte proliferation, hydrophilic BA such as UDCA protect against apoptosis while hydrophobic BA such as TLCA and GCDCA cause hepatic apoptosis and liver injury.[6,10]

UDCA has been used as therapy in cholestasis for centuries. The ancient Chinese medicine utilized a powder derivate from dried bile of adult bears for the management of hepatobiliary disorders.[12] UDCA results in the displacement of endogen hydrophobic BA pool to hydrophilic and protective BA pool competition for absorption in the ileum.[13] Moreover, UDCA modulates membrane transport proteins increasing intracellular Ca^{2+}, Cl^- efflux and bicarbonate influx into bile; immunomodulatory effects and activation of PKC and MAPK signalling have been also considered in mitigating liver injury.[13]

During pregnancy the woman's body is exposed to several modifications such as plasma volume increment, cardiovascular changes, increased need for nutrients and metabolism rearrangements.[14-18] Metabolic adaptations include a gradual rise of serum BA; an increase which is usually slight and doesn't exceed the normal ranges.[19] However, a little portion of women experiences cholestasis (ICP) which is the most common liver disease during pregnancy with a prevalence greatly varying between ethnic groups and about of 0.3% to 0.7% in Western Europe.[20,21] ICP diagnosis is raised if BA levels >10 µmol/l (fasting) or >14 µmol/l (postprandial) or the patient has pruritus and elevated transaminase levels, after exclusion of other conditions.[20] Maternal prognosis is benign going to resolution after delivery, although pruritus can be struggling and resulting in insomnia and mental stress. Pruritus intensity is positively associated with autotaxin activity and lysophosphatidic acid (LPA) and serum autotaxin levels may be useful for the differential diagnosis between ICP and other pathologies.[22] Nevertheless, BA accumulation in the placenta, fetus and amniotic fluid may be harmful for the baby with severe complications such as prematurity, fetal distress and even intrauterine fetus loss.[23,24] Fetal death may subsequent to fetal dysrhythmia. In fact, while glycine-conugates are predominant in normal pregnancy, taurine-conjugates are elevated in ICP; taurocholate is toxic and in a rat model the addition of taurocholate to primary cultures of cardio-myocytes resulted in abnormal contraction and calcium dynamics.[25,26] Furthermore, dysfunctional fetal cardiac phenotype is associated to high level of maternal serum BA and UDCA treatment during pregnancy maybe cardioprotective for the fetus.[27] Beyond the fact that it is routinary to administer UDCA therapy, it is not clear if it can actually improve the fetal outcomes and hypotheses are controversial although it may ameliorates maternal symptoms.[21,28,29] There is a correlation between fetal complications and maternal BA levels with a 1%-2% increased probability of preterm delivery, asphyxia events and amniotic fluid stained by meconium for each additional µmol/l of BA exceeding 40 µmol/L and an increased probability of green-staining of placenta membranes for additional µmol/l of BA exceeding 20 µmol/l.[24] Preterm delivery maybe caused by a more intense cells response to oxytocin stimuli in ICP than healthy woman since in vitro studies showed an increased oxytocin-receptor expression in myometrial cells after incubation with cholic acid.[30,31] Risk factors for ICP are liver disease such as hepatitis C and B or cholelithiasis, multiple pregnancy, assisted reproductive technology, nutritional deficits such as vitamin D and selenium insufficiency, and most likely genetic predisposition such as variation in the ABCB4 and ABCB11 genes encoding the phosphotadidylcholine floppase MDR3 and the BA efflux pump BSEP, accounting for 10%-15% of cases in Europe.[22,32-34] Ormonal factors may concur to the ICP onset; in fact, for example, activation of the estrogen receptor-α induces a downregulation of the BA efflux pump BSEP expression

in in vitro and murine models.[22] Risk of recurrence after ICP in previous pregnancy is about 45-70%.[21]

Several techniques can be applied to measure serum BA.[35] While mass spectrometry and liquid chromatography can measure total and fractions serum BA, enzymatic assays are able to quantify only total BA but advantageously can be used in fully-automated clinical chemistry platform making the test suitable for routinary clinical use.[36] Our laboratory assay utilizes the enzymatic cycling method where BA in the sample are converted to their corresponding oxosteroids in the presence of excess nicotinamide adenine dinucleotide (NADH) and thionicotonamide adenine dinucleotide (thio-NAD+). The enzyme 3α-hydroxysteroid dehydrogenase (3α-HSD) oxides primary, secondary and tertiary BA to 3α-oxosteroids. Thio-NAD+ is concomitantly reduced to thio-NADH (404 nm) in proportion to the concentration of BA present in the sample.

However, accordingly to the method, medication with the tertiary bile acid ursodeoxycholic acid may lead to falsely high levels of total BA. After experiencing this clinical case, our laboratory decided, to introduce on the laboratory report a warning note alerting the patient and the clinician that ursodesoxycholic acid (UDCA) therapy may interfere with the total bile acid assay and it is recommended to discontinue the administration 24 hours before the blood draw.

Elevated BA levels could be dangerous for the fetus being associated to fetal complications, perinatal mortality rates, stillbirths, low birthweight, preterm labour and birth, increased incidence of meconium-stained amniotic fluid and fetal distress. Such complications are more common for BA levels >40 µmol/l.[29] Cut-off values for stillbirth varies from 40 to 99 µmol/l[21] and a BA level ≥100 µmol/l is a predictive marker for stillbirth.[21]

According to SIGO and AOGOI Italian guidelines and to those published by the Society for Maternal-Fetal Medicine and the Royal College of Obstetricians and Gynaecologists, there is indication for induction of labor and delivery between the 35th and 36th weeks of pregnancy for BA ≥100 µmol/l, between the 37th and 38th weeks of pregnancy for BA between 40 and 99 µmol/l and at 39th week of pregnancy if BA<40 µmol/l.[37] Ultimately, bile acid values >40 µmol/l could be dangerous for the fetus and should be promptly brought to the attention of the gynecologist. The laboratory performs a pivotal function for clinical decisions and the link clinic-laboratory is crucial.[38] Alarm values communication is critical and is the key to timely and effective potentially life-saving clinical intervention. The College of American Pathologists (CAP) requires precise rules and a high quality system that can ensure the reporting of alarm values in all laboratories but there is no list of critical values that can be shared across all laboratories.[39] This is because of differences in patient population, clinical demand, instrumentation and organization; however, each laboratory should draw up a list of critical values that is appropriate in its context and can be used for high-level health delivery.

SIBioC-SIMeL-CISMEL Intersociety Study Group on extra-analytical variability of laboratory data also recommends to realize a list of panic values and define criteria for their communication.[40]

The main problems in establishing suitable procedures for managing critical values are related to the insufficiency of definitive information to determine the effectiveness of including a parameter in the list of potential critical values and the resulting magnitude of deviation in order to be considered truly critical. The development of a list of critical values consistent with the local laboratory environment and the adoption of an efficient and standardized procedure for reporting critical values is imperative. Our hospital which represents an excellence in the Italian and the European context of pediatric medicine and is accredited by the Joint Commission International (JCI), has a critical value list specific for its setting and follows standardized procedures for reporting critical laboratory data for both inpatients and outpatients. However, our laboratory works predominantly pediatric data, and alerts on BA levels in serum of pregnant women had not been considered in our laboratory's list of alert values. As part of the correction actions implemented after this case, an alert value for BA >40 µmol/l in female patients aged >18 years old was included in our list.

CONCLUSION

In conclusion, although the patient was not found to have severe ICP but only a mild ICP and therefore did not have fetal complications because the BA level was falsely elevated due to UDCA therapy assumption, our laboratory promptly introduced a critical value for serum BA for outpatient population potentially pregnant, in order to prevent adverse events and to provide the best possible health service for the protection of the mother and child.

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