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Original Contribution

The incidence of coagulopathy in pregnant patients with intrahepatic cholestasis: should we delay or avoid neuraxial analgesia?☆

Alexander DeLeon MD (Assistant Professor)[a,*], Gildasio S. De Oliveira MD, MSCI (Assistant Professor Associate Chair for Research)[a], Manoj Kalayil MD (Obstetric Anesthesia Fellow)[a], Shweta Narang MD (Resident in Anesthesiology)[b], Robert J. McCarthy PharmD (Research Professor)[a], Cynthia A. Wong MD (Professor)[a]

[a]*Department of Anesthesiology, Northwestern University, Chicago, IL 60611, USA*
[b]*Department of Anesthesiology, John H. Stroger, Jr., Hospital of Cook County, Chicago, IL 60612, USA*

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Abstract

Study Objective: To estimate the incidence of coagulopathy in patients with intrahepatic cholestasis inhepatic cholestasis of pregnancy (ICP).

Design: Retrospective cohort investigation.

Setting: University medical center.

Measurements: The records of 319 parturients who met study inclusion criteria were reviewed for various laboratory values. The primary outcome was the incidence of abnormal hemostasis, defined as prothrombin time (PT) greater than 14.5 seconds (INR > 1.2). The incidence of postpartum hemorrhage was evaluated as a secondary outcome.

Main Results: The incidence (95% CI) of abnormal PT was 0% (0 to 1.8). Other coagulation tests [partial thromboplastin time (PTT) and platelet count] were also normal, even in study subjects with significant (>5 times) elevation of liver enzymes. The incidence of postpartum hemorrhage after vaginal delivery was 2.4% (4 of 208 pts) and 6.3% (7 of 111 pts) after Cesarean delivery.

Conclusions: Coagulation abnormalities are rare in pregnant patients with ICP, even when a strict criterion is utilized (INR < 1.2). The use of neuraxial anesthesia and/or analgesia may not necessarily be delayed in parturients with isolated ICP.

1. Introduction

Many women request analgesia for labor or require surgical anesthesia for Cesarean delivery [1,2]. The American College of Obstetricians and Gynecologists has stated that

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* Correspondence: Alexander M. DeLeon, MD, Assistant Professor and Associate Chair, Department of Anesthesiology, Feinberg School of Medicine, Northwestern University, 241 East Huron St., F5-704, Chicago, IL 60611, USA. Tel.: +1 312 695 0116.
E-mail address: adeleon@northwestern.edu (A. DeLeon).

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neuraxial analgesia is the most flexible, effective, and least depressing analgesic modality to the central nervous systems of both the mother and the baby [3]. Delaying neuraxial analgesia may cause significant patient distress and suffering, especially when optimal analgesia is not achieved with systemic medications or other regional techniques [4–7]. Due to the risk for spinal-epidural hematoma, parturients with diseases that may potentially adversely affect hemostasis are frequently denied neuraxial analgesia until abnormal coagulation is excluded by laboratory examination. A coagulopathy is considered a contraindication to neuraxial procedures because of the potential catastrophic consequences of spinal-epidural hematomas [8–10].

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease unique to pregnancy, with a reported incidence as high as 4% [11]. Patients with ICP have steatorrhea from fat malabsorption, which may adversely affect vitamin K absorption and impair coagulation [12]. In addition, the disease may cause transient liver damage, which may further impair coagulation. Small studies (≤ 100 subjects) examined the incidence of coagulopathy, evaluated by a prolonged prothrombin time (PT) in women with ICP and showed conflicting results, but the incidence of abnormal coagulation tests has been as high as 20% [13,14]. Since the incidence of coagulopathy in patients with ICP is currently not well defined, some practitioners often delay neuraxial techniques in those patients until laboratory exclusion of abnormal hemostasis is obtained.

The main objective of the current investigation was to estimate the incidence of coagulopathy in women with ICP and to determine if the presence of abnormal liver function in patients with ICP was associated with a higher incidence of abnormal coagulation tests.

2. Materials and methods

The study was a retrospective cohort investigation. Approval for the study was obtained from the Northwestern University Institutional Review Board. Parturients with a possible diagnosis of ICP were identified by searching the Northwestern Medical Enterprise Data Warehouse using ICD-9 codes (646.70, 646.71, 646.73, and 576) from the years of 2005 to 2009, followed by individual chart reviews by two investigators (AD and MK) to confirm the diagnosis and exclude other liver diseases. Exclusion criteria included patients with preexisting liver disease, coexisting obstetric conditions associated with risk for coagulopathy (preeclampsia, eclampsia, and placental abruption), other known coagulation factor abnormalities (qualitative or quantitative), and anticoagulant used during pregnancy.

Data extracted from the database included subjects' demographic characteristics (age, body mass index, ethnicity), gravidity, parity, delivery mode (vaginal, Cesarean), laboratory coagulation values [PT, partial thromboplastin time (PTT), and platelet count], estimated blood loss (EBL), and liver function tests [aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase]. The liver function tests were drawn either during a prenatal visit or during labor. All coagulation studies included in the analysis were drawn during labor prior to delivery. Postpartum hemorrhage was defined as an EBL greater than 500 mL after vaginal delivery and greater than 1000 mL after Cesarean delivery, as reported by the obstetrician in the delivery note.

The primary outcome was the presence of an abnormal PT value [defined as PT > 14.5 sec (INR > 1.2)]. This value was chosen because the American Society of Regional Anesthesia guidelines recommended that the INR be normal before initiating neuraxial anesthesia in a previously anticoagulated obstetric patient [14].

An *a priori* sample size analysis determined that a sample size of 200 subjects with ICP would result in 40 patients with abnormal PT values, assuming a 20% incidence of disease [13]. This sample size allowed construction of a multivariate model with three variables, with a conservative rate of one variable for 15 events [15].

The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test the hypothesis of normal distribution. Normally distributed interval data are reported as means (SD) and were evaluated with Student's t-test for equal variances. Non-normally distributed interval and ordinal data are reported as medians [ranges or interquartile ranges (IQR)] and compared among groups using the Mann-Whitney U test [16]. Categorical variables are presented as numbers and analyzed with Fisher's Exact test. All reported *P*-values are two-tailed. The criterion for rejection of the null hypothesis was a two-tailed $P < 0.05$.

3. Results

Three hundred nineteen patients met the study inclusion criteria, 223 of whom underwent coagulation tests. Demographic characteristics of parturients with ICP who had and did not have coagulation tests prior to delivery are presented in Table 1. The incidence (95% CI) of abnormal PT (INR) in the parturients with ICP was 0% (0 - 1.8%). Other coagulation tests were also normal in all subjects (Fig. 1).

Thirteen patients had liver enzymes (ALT and/or AST) values greater than 5 times normal but none had abnormal coagulation tests (PT, PTT, and platelets). Estimated blood loss and mode of delivery did not differ between the parturients with ICP who had coagulation tests checked before delivery and those whose coagulation tests were not checked (all $P > 0.05$) (Table 1).

Of the subjects who received a neuraxial technique, none suffered a neuraxial hematoma. The incidence of postpartum hemorrhage was 4 of 208 (2.4%) patients after vaginal delivery and 7 of 111 (6.3%) patients after Cesarean delivery.

Table 1 Characteristics of parturients with intrahepatic cholestasis with and without coagulation tests

	No coagulation tests checked (n = 96)	Coagulation tests checked (n = 223)	*P*-value
Age (yrs)	34.3 ± 6.1	33.3 ± 6.1	0.16
Body mass index (kg/m^2)	29.2 ± 4.2	30.2 ± 5.6	0.11
Race			0.94
white	56	131	
African-American	4	12	
Asian	4	7	
other/not specified	32	73	
Gestational age (wks)	37.2 (36.8 - 38.1)	37.2 (37 - 38)	0.56
Parity			0.54
nulliparous	45	113	
parous	51	110	
Delivery mode			0.79
vaginal	32	79	
Cesarean	64	144	
Estimated blood loss (mL)			0.57
< 500	68	149	
501-1000	24	67	
1001-1500	3	3	
1501-2000	1	4	

Values are numbers, means ± SD, or means (ranges).

4. Discussion

The most important finding of the current investigation was the lack of abnormal coagulation studies in parturients with ICP. Even patients with evidence of significant liver damage (enzyme elevations greater than 5 times normal) did not have abnormal coagulation tests. No neuraxial hematoma complications were detected and the incidence of abnormal bleeding after delivery was consistent with the incidence reported in the literature for healthy obstetric patients [17–19]. Taken together, our results do not support routine coagulation test monitoring in parturients with ICP to minimize neuraxial procedure complications or predict postpartum hemorrhage.

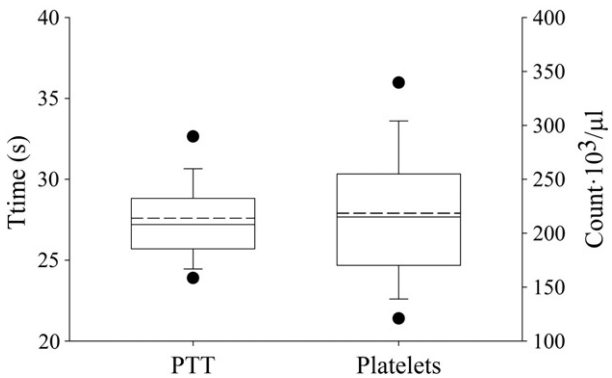

Fig. 1 Box plot demonstrating normal results of coagulation tests in the study population. Median response = horizontal bar and interquartile range (IQR) = boxes. Horizontal dotted lines = mean values. Whiskers = 10th and 90th percentiles of the data; circles = outliers. PTT = partial thromboplastin time.

Previous research has reported a much greater incidence of abnormal coagulation tests in parturients with ICP than the current one [13]. The reason these results differed from other reports is unclear, although it is possible that institutional differences exist in the diagnosis of ICP. In addition to the cost associated with unnecessary laboratory tests, labor analgesia may be delayed. Delayed labor analgesia may substantially decrease patient satisfaction and increase the risk for general anesthesia in the event that urgent intrapartum Cesarean delivery is necessary [20–22].

Among the parturients with ICP, the patient characteristics that influenced anesthesiology providers' decisions to order coagulation tests before neuraxial anesthesia could not be identified. Since cholestasis of pregnancy may harm the fetus, delivery at 37 weeks or earlier, depending on the severity of the disease, has been recommended [23,24]. Gestational age was not a potential marker for the severity of ICP in this study population. This fact supports the theory that individual provider rather than severity of the disease was likely the reason for assessing coagulation tests in this patient population.

It is important to note that patients with other liver diseases, pregnancy-related coagulation abnormalities, or other primary coagulopathies were excluded from analysis. A negative synergistic effect of ICP and other pregnancy-related coagulopathies such as preeclampsia on the coagulation system may not be excluded [25,26]. Clinical practitioners should be attentive to the potential synergistic increased risk when more than one condition

associated with coagulation abnormalities is present in the same patient.

Intrahepatic cholestasis of pregnancy frequently appears during the second or third trimester of pregnancy. The pathogenesis of the disease is largely unknown but seems to be related to increased hepatic metabolism of estrogen and/or progesterone during pregancy [12]. Disease progression is benign for most women, but it may have severe health consequences for the fetus [23]. Treatment with ursodeoxycholic acid seems to have the best response against pruritus in those patients and may reduce perinatal complications [24].

The study should only be interpreted in the context of its limitations. First, routine coagulation test (PT, PTT, and platelet count) were examined and it is possible that more sophisticated coagulation testing would have detected coagulation abnormalities in parturients with ICP [27–29]. Nevertheless, the routine evaluation of patients' suitability for neuraxial anesthesia is based primarily on routine coagulation tests (PT, PTT, and platelet count). Second, the study was retrospective and, like other retrospective studies, selection bias may not be excluded [30,31]. Finally, since ICD-9 codes were used to identify cases of ICP, it is possible that mild forms of the disease may have been underrepresented in the study population; however, it is unlikely that patients with mild disease would have suffered abnormalities of the coagulation system.

In summary, the incidence of coagulopathy in parturients with isolated ICP is extremely low. Abnormal hemostasis was not detected even in parturients with significant elevation of liver enzymes, further supporting the argument that routine coagulation studies are not necessary. Clinicians may consider restricting the need for additional coagulation studies in patients with ICP to those with coexisting diseases (eg, preeclampsia, liver diseases).

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