**Pediatr Pract Res** 2023; 11(3): 177-181
**DOI:** 10.21765/pprjournal.1355747

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

# The Outcome of Maternal and Fetal Cases with Intrahepatic Cholestasis of Pregnancy

## Gebelikte İntrahepatik Kolestazolan Vakaların Maternal ve Neonatal Sonuçları

**Zuat Acar[1], Yunus Cavus[2], Yusuf Başkıran[3]**

[1]Department of Obstetrics and Gynecology İstanbul Tema Hospital, İstanbul, Turkey
[2]Department of Obstetrics and Gynecology İstanbul Gelişim University, İstanbul, Turkey
[3]Department of Obstetrics and Gynecology Yüzüncü Yıl University, Van, Turkey

## ABSTRACT

**Aim**: Intrahepatic cholestasis (ICP) of pregnancy is a common disorder of pregnancy manifested by pruritus and elevated bile acids.Some negative obstetric outcomes of ICP; Spontaneous preterm birth, meconium amniotic fluid, fetal asphyxia and stillbirth have been reported in the literature. Due to the lack of evidence for diagnosis, treatment, and concomitant adverse outcomes, management has two main goals: reducing troubling symptoms and perinatal morbidity and mortality.

**Material and Method**: Medical records of patients diagnosed and followed up with intrahepatic pregnancy cholestasis between January 2017 and June 2021 were reviewed retrospectively.

**Results**: The mean week of delivery of the patients was 38.1±1.4, and no fetal or neonatal death occurred during their follow-up.

**Conclusion**: With respect to the increased risk of adverse neonatal outcomes and stillbirth in patients with ICP, timing of birth in maternal ICP patients should be carefully evaluated. In conclusion, there is some evidence to suggest that birth at 37$^{th}$ weeks, especially in patients with severe bile acid level elevations, may improve outcomes. However as a result of this study in which the average gestational age at birth was 38 weeks and no fetal mortality occurred, we suggest that with close monitoring and early administration of treatment birth at 38 weeks could potentially improve outcomes in patients with low bile acid levels. Furthermore, optimal timing for birth in patients with ICP is as of yet unknown, due to the absence of randomized studies evaluating elective early induction of labor.

**Keywords**: Intrahepatic cholestasis, pregnancy, neonatal outcomes, bile acid, stillbirth,

## ÖZ

**Amaç**: Gebelikte intrahepatik kolestaz (ICP), kaşıntı ve safra asitlerinin yükselmesi ile kendini gösteren, gebelikte sık görülen bir hastalıktır. ICP'nin bazı olumsuz obstetrik sonuçları; Literatürde spontan erken doğum, mekonyumlu amniyotik sıvı, fetal asfiksi ve ölü doğum bildirilmektedir. Tanı, tedavi ve eşlik eden olumsuz sonuçlara ilişkin kanıtların bulunmaması nedeniyle, tedavinin iki ana hedefi vardır: rahatsız edici semptomları ve perinatal morbidite ve mortaliteyi azaltmak.

**Gereç ve Yöntem**: Ocak 2017 ile Haziran 2021 tarihleri arasında intrahepatik gebelik kolestazı tanısı konularak takip edilen hastaların tıbbi kayıtları geriye dönük olarak incelendi.

**Bulgular**: Hastaların ortalama doğum haftası 38,1±1,4 olup, takipleri sırasında herhangi bir fetal veya neonatal ölüm yaşanmadı.

**Sonuç**: İCP'li hastalarda olumsuz neonatal sonuçlar ve ölü doğum riskinin artması nedeniyle, anne İCP'li hastaların doğum zamanlaması dikkatle değerlendirilmelidir. Sonuç olarak, özellikle ciddi safra asidi yüksekliği olan hastalarda 37. haftada doğumun sonuçları iyileştirebileceğini gösteren bazı kanıtlar vardır. Ancak doğumda ortalama gebelik yaşının 38 hafta olduğu ve fetal mortalitenin görülmediği bu çalışmanın sonucunda, yakın takip ve tedavinin erken uygulanmasıyla 38. haftada doğumun düşük safra asidi düzeyi olan hastalarda sonuçları potansiyel olarak iyileştirebileceğini düşünüyoruz. Ayrıca, ICP'li hastalarda doğumun optimal zamanlaması, elektif erken doğum indüksiyonunu değerlendiren randomize çalışmaların bulunmaması nedeniyle henüz bilinmemektedir.

**Anahtar Kelimeler**: İntrahepatik kolestaz, gebelik, yenidoğan sonuçları, safra asidi, ölü doğum,

**Corresponding Author:** Zuat ACAR
**Address:** Department of Obstetrics and Gynecology İstanbul Tema Hospital, İstanbul, Turkey
**E-mail:** drzacar@hotmail.com

**Başvuru Tarihi/Received:** 05.09.2023
**Kabul Tarihi/Accepted:** 07.10.2023

## INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a reversible cholestasis characterized by pruritus with elevated serum bile acid concentrations and/or liver enzymes, usually beginning in the second or third trimester, without other liver diseases and chronic diseases (1). There is no agreement on diagnostic criteria for ICP. Levels of liver tests such as bile acids/salts level, AST, ALT, bilirubin, GGT can be very variable. Liver enzymes (AST-ALT) are elevated in ~60% to 85% of ICP patients. The elevation of liver enzymes (transaminases) less than twice the upper limit of normal distinguishes it from other liver diseases such as viral hepatitis and preeclampsia in pregnancy (2). The mean AST, ALT, and GGT levels in the study were 86.9±36.4, 110.5±63.6, and 55±22.9, respectively. Bile acid level for diagnosis in ICP patients South Australian Maternal and Neonatal Practice Association (SAMNCP) guideline, it was determined as 15 µmol/L, while it was determined as 10 µmol/L by the American College of Gastroenterologists (ACG). Since the limit was determined as 10 µmol/L in most studies, it was determined as 10 µmol/L in our study (3).

ICP may affect approximately 0.3-5.6% of pregnancies and may differ by ethnicity, geographic region, and seasonality (4). Although the etiology is not known exactly, increased estrogen levels during pregnancy and related changes in protein expression are possible causes. (5). In general, ICP begins in the third trimester, when circulating estrogen and progesterone levels are highest, supporting that hormone levels affect cholestasis (6,2) Most sources agree on the importance of itching and abnormal liver function (6,2). Itching usually begins 3 weeks before diagnosis and usually occurs without an increase in bile acid levels. (2) Resolution of ICP is spontaneous after birth, but women with a history of ICP have hepatobiliary and cardiovascular disease with advancing age (7,8). Some negative obstetric outcomes of ICP; Spontaneous preterm birth, meconium amniotic fluid, fetal asphyxia and stillbirth have been reported in the literature. (9-11). Despite the associated adverse outcomes, opinions regarding appropriate diagnostic criteria, maternal and fetal surveillance, treatment, and timing of delivery vary (12). The relative rarity of this condition, coupled with different guidelines, complicates management decisions for busy clinicians.

Due to the lack of evidence for diagnosis, treatment, and concomitant adverse outcomes, management has two main goals: reducing troubling symptoms and perinatal morbidity and mortality. reduce the risk (13). Ursofalk (ursodeoxycholic acid) is the most commonly used treatment for ICP. Ursodeoxycholic acid has been reported to lower bile salt levels in other tissues, including amniotic fluid and cord blood. After UDCA administration, it results in reduction in pruritus in ~60% of women and complete relief in ~40% of women (14). Symptoms typically resolve within 1-2 weeks of initiation of therapy, and a decrease in serum bile acids occurs after 2 weeks. Several studies have been conducted to evaluate the efficacy of UDCA in the treatment of pruritus, normalization of liver transaminases, and reducing the risk of poor perinatal outcome. UDCA improves pruritus, serum bile salt levels, and may reduce potential intrauterine fetal outcomes, but data on perinatal outcomes are limited (12,14-16)

The aim of this study is to examine the pregnancy results of 50 patients who developed intrahepatic cholestasis during pregnancy in the light of the literature, to discuss the current risks and how the pregnancy follow-up plan should be.

## MATERIAL AND METHOD

The study was carried out with the permission of İstanbul Gelişim University Ethics Committee (Date: 10/06/20121, Decision No: 2021-21). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The medical records of patients who were followed up with the diagnosis of intrahepatic pregnancy cholestasis in a tertiary center between January 2017 and June 2021 were reviewed retrospectively. For the diagnosis of intrahepatic cholestasis of pregnancy: Having a 3rd trimester pregnancy ,widespread pruritus not due to a dermatological pathology, laboratory findings supporting ICP findings (AST-ALT > 40 U/L), ultrasonographically normal liver and gallbladder, negative serology hepatitis A, B, C, fasting bile acid level > 10 µmol/L conditions were sought. After diagnosis, Ursodeoxycholic acid 750 mg (UDCA) (Ursofalk 250 mg capsule) was started. Presence of preeclampsia or hypertension, any pre-pregnancy liver disease and a history of disease with liver involvement were considered as exclusion criteria.

Patients diagnosed with ICP were followed up in the outpatient clinic with weekly liver function tests (KFT), amniotic fluid index (ASI) evaluations and weekly non-stress tests (NST). In case of clinical progression (increased itching, jaundice), elevated LFT values and abnormal NST findings, the patient was hospitalized and NST, ASI, LFT, coagulation and bleeding profiles were monitored every other day. All of the patients were evaluated in terms of hepatic-biliary tract pathology with upper abdominal ultrasonography and hepatitis A, B and C were found to be negative in all of them. Bile acid levels were measured after fasting. Delivery was planned for patients who were hospitalized and had liver enzymes increased more than 10 times, lost variability or had a slowed NST during their follow-up. The cases were evaluated according to the criteria of time of delivery, mode of delivery, perinatal morbidity and mortality, preterm delivery and neonatal complications.

SPSS 22.0 statistical program was used for analysis in our study. Mean, standard deviation, minimum and maximum values were used from descriptive statistics.

## RESULT

Fifty patients with pregnancy-related intrahepatic cholestasis were included in the study. The mean age of the patients, BMI (Body mass index), AST-ALT, GGT, T BL-D BL, ALP, GGT, fasting bile acid level, infant weight, Apgar scores, meconium contamination in amniotic fluid, cholestasis diagnosis time, method of administration and time was examined (**Table 1**). The mean age of the patients was 30.1±5.1 years, 50% of them gave birth for the first time. BMI was 24.9±3.1. Abdominal USGs of all patients were normal at the time of diagnosis. Mean AST, ALT, and GGT levels were 86.9±36.4, 110.5±63.6, and 55±22.9, respectively. When the patients were diagnosed, the mean gestational week was 30.5±3.4, and the mean delivery time was 38.1±1.4. Preeclampsia was found in 1.52% (n:3) and gestational diabetes (GDM) in 16% (n:8) of the patients. Itching was reported in 79% of patients admitted to the hospital. It was determined that the patient's complaints regressed in the 1st week postpartum.

**Table 1: Patient characteristics and laboratory results**

| | Pregnant with cholestasis n:50/SD |
|---|---|
| Age | 30.1±5.1 |
| BMI | 24.9±3.1 |
| AST | 86.9±36.4 |
| ALT | 110.5±63.6 |
| T.BIL | 0.94±0.83 |
| D.BIL | 0.50±0.70 |
| ALP | 71.9±22.1 |
| GGT | 55±22.9 |
| Bile Acids | 17.5±28.1 |

SD: Standard deviation

The mean week of diagnosis of the patients was 31.5±3.4, and the mean week of delivery was 38.1±1.4. (**Table 2**). The diagnosis period of 1 (in vitro fertilization patient) patient was 6. It was determined that 76% (n:38) of the patients were delivered by cesarean section, 24% (n:12) were delivered vaginally, and 16% (n:38) were delivered vaginally: 38%(n=8) of the patients gave birth before 38 weeks. When the postpartum results were examined, it was found that 8 fetuses (24%) had an Apgar score below 7 at the 1st minute at birth, and 4 fetuses (12%) had an Apgar score below 7 at the 5th minute. and no neonatal death was found. The rate of hospitalization in the neonatal intensive care unit was 10% (n=5), and the most common cause was prematurity. The rate of RDS (respiratory distress syndrome) was 6%(n=3). Meconium contamination was detected in the amniotic fluid of 18 (36%) patients. Meconium aspiration was detected in an infant hospitalized in the neonatal intensive care unit. Thirty (60%) newborns were girls and 20 (40%) were boys. There were no complications in the follow-ups. Due to the development of hepatocellular carcinoma in the follow-up of one patient, his treatment is still continuing in the medical oncology unit.

**Table 2: Neonatal outcomes of ICP patients**

| | (Minimum-maximum) | Mean |
|---|---|---|
| Diagnosis time | 6-34.1 weeks | 31.5±3.4 |
| Time of delivery | 33.5-40.3 weeks | 38.1±1.4 |
| Birth weight | 1480-3750 | 3126±413 |
| Apgar 1. Bw | 4-9 | 8.06±0.9 |
| Apgar 5. Bw | 6-10 | 9.76±0.7 |

## DISCUSSION

Intrahepatic cholestasis of pregnancy, adversely affecting maternal and neonatal outcomes, is the most common gestational liver disease (1, 3, 16). This paper aims to reassess this significant cause of fetal morbidity, mortality, and negative obstetric consequences with perspective garnered in recent literature. Wikström et al. Published a study concerning patients with ICP in 2013, showing that patients with ICP were at a 2.8 fold risk of gestational diabetes (GDM), and a 2.6 fold risk of preeclampsia compared to patients without ICP (17). Throughout the study, 8 (16%) of followed up patients were diagnosed with GDM, while 3 were diagnosed with preeclampsia. Patients with ICP have a significantly increased risk of fibrosis, cholangitis, hepatitis C, gallstone disease, hepatobiliary cancer, cardiovascular disease, and immune mediated diseases (7). One patient in our study was diagnosed with hepatocellular carcinoma and is currently undergoing treatment.

Aside from effects on maternal health, ICP's impact on fetal health cannot be understated. Meconium contamination of amniotic fluid, premature births, fetal distress, and intrauterine fetal mortality are among the negative events associated with ICP. With regards to meconium contaminated amniotic fluid, gall has been shown to directly stimulate intestinal motility in animal studies (18). A meta-analysis carried out on patients with ICP complications during pregnancy showed that the incidence of meconium contamination was increased from ~11% to 19% (4). Our study found that 18 (36%) patients had confirmed meconium contamination, a figure significantly higher than in preceding literature. Neonatal hypoxia was not observed in these patients, nor was it associated with negative fetal outcomes. This increased incidence of meconium contamination could be attributed to the fact that ICP patients in the literature, in contrast to patients in our study,were brought into labor before at the 37th week. Though no clear explanation is put forward by the current literature, we hypothesize that neonatal bile acids may

have increased intestinal motility, as it did in our study. This topic requires more detailed investigation in future studies.

Another condition associated with ICP is respiratory distress syndrome (RDS). Although increased RDS incidence is likely explained at least in part by both spontaneous and iatrogenic preterm labor, animal models have demonstrated a causative association. In a rabbit model, bile acids injected directly into the trachea were shown to cause atelectasis, eosinophilic infiltration, and hyaline membrane development which was reversed through administration of surfactants.

In a swine model, bile acids were shown to cause serious chemical pneumonitis and lung edema (10). In the present study, RDS risk was found to be 6%, similar to the risk of RDS in non-complicated pregnancies in the literature. RDS was found to be especially associated with low weight births.

Fetal mortality is the most severe complication of ICP. High bile salt levels' association with stillbirth was found to possess a relative risk ratio of 2.6, consistent with current literature (8, 9). The mechanism behind fetal mortality in patients with ICP is not well understood. Negative fetal outcomes in patients with ICP have been associated with elevated levels of bile acids in amniotic fluids, cord blood, meconium, as well as elevated bile salt levels in the fetal compartments (9). Aside from the association with chronic placental insufficiency, bile acids' effects on the fetal heart are hypothesized to be directly related to fetal mortality. Clinical studies aiming to study the arrhythmogenic effect of bile acids on the fetal heart reported an increased incidence of fetal atrial flutter and supraventricular tachycardia in ICP patients. In human and animal myocytic stem cell studies, administration of bile salts was shown to decrease contractility and cause arrhythmia. In the same studies, ursodeoxycholic acid therapy was shown to prevent this effect (20). The absence of fetal mortality in the studies may be explained by close monitoring of fetal well-being and cardiac activity, as well as early administration of UDCA therapy.

In one study investigating intrauterine and postnatal outcomes, though threshold diagnostic values for bile acid vary, patients with bile acid levels above 40 µmol/L were defined as having severe cholestasis, and this was associated with adverse perinatal outcomes (11). More research assessing adverse intrauterine fetal outcomes in ICP patients showed that perinatal mortality risk in patients with bile acid levels over 100 µmol/L was 30 times higher than in patients with levels under 40 µmol/L (4). In line with findings in the literature, our threshold diagnostic value for cholestasis was defined as 10 µmol/L, and patients over this limit were diagnosed with ICP. The average bile acid level in our study was found to be 17.5±28.1. Roughly 20% of patients with ICP had bile acid levels over 40 µmol/L. Low overall bile acid levels can likely be attributed to early administration of treatment. One emergency ceasarean section was carried out in the 34th gestational week due to fetal distress in patient with high bile acid levels (211 µmol/L). We attribute the absence of fetal mortality in our study to the lack of severe cholestasis (<40 µmol/L), likely due to early treatment of patients.

Birth related perinatal mortality risk has been shown to increase from the 36th gestational week onwards; due to this, elective preterm birth is commonplace in the management of ICP patients (21). Patients followed up through the 39th week, as well as patients followed up on a weekly observation basis have been shown to have a higher risk of perinatal mortality compared to patients managed in the aforementioned way in the 36th week (21). These findings support previous studies suggesting that fetal mortality rates increased after the 36th gestational week. No fetal monitoring method has been shown to be effective in predicting negative perinatal outcomes or reducing risk of stillbirth. An explanation for this, as discussed previously, is that anoxic events may occur acutely rather than chronically. Despite a lack of evidence that antenatal testing is beneficial to fetal health, use of antenatal testing continues to be commonplace. In a study conducted among obstetric healthcare providers in the United Kingdom, 95% of maternity wards that responded to the study stated that they utilized fetal monitoring (15).

The American Congress of Obstetricians and Gynecologists recommends late preterm and preterm birth in the 36th - 37th gestational weeks. Furthermore, birth prior to the 36th week in patients with select clinical and laboratory parameters has been proposed (22,23). On the other hand, The Royal College of Obstetricians and Gynecologists has remained impartial, stating that practices developed for use at 37 weeks are not supported by evidence (5). The average gestational age at birth in our study was 38.1±1.4. In the event of adverse biochemical or clinical parameters, NST, AFI, and LFT's were carried out and births were planned with respect to the patients' health. The main limitations of this study were the absence of fetal mortality, relatively small number of patients, and a lack of understanding of bile salt levels. Despite this, early administration of treatment may account for the absence of fetal mortality. Additionally, this may be explained by (with the exception of one patient) absence of elevated serum bile acid levels.

## CONCLUSION

With respect to the increased risk of adverse neonatal outcomes and stillbirth in patients with ICP, timing of birth in maternal ICP patients should be carefully evaluated. In conclusion, there is some evidence to suggest that birth at 37th weeks, especially in patients with severe bile acid level elevations, may improve

outcomes. However, as a result of this study in which the average gestational age at birth was 38 weeks and no fetal mortality occurred, we suggest that with close monitoring and early administration of treatment birth at 38 weeks could potentially improve outcomes in patients with low bile acid levels. Furthermore, optimal timing for birth in patients with ICP is as of yet unknown, due to the absence of randomized studies evaluating elective early induction of labor.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of İstanbul Gelişim University Ethics Committee (Date: 10/06/20121, Decision No: 2021-21).

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients for the study.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

## REFERENCES

1. Clinical Updates in Women's Health Care Sum- mary: Liver Disease: Reproductive Considerations. Obstet Gynecol 2017;129:236.
2. Chen Y, Vasilenko A, Song X, et al. Estrogen and estrogen receptor-α-mediated transrepression of bile salt export pump. Mol Endocrinol. 2015;29:613–26.
3. Manzotti C, Casazza G, Stimac T, et al. Total serum bile acids or serum bile acid profile, or both, for the diagnosis of intrahepatic cholestasis of pregnancy. Cochrane Database Syst Rev. 2019;7:1-90.
4. Ovadia C, Seed PT, Sklavounos A, et al. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of aggregate and individual patient data meta-analyses. Lancet. 2019;393:899–909.
5. Bicocca MJ, Sperling JD, Chauhan SP. Intrahepatic cholestasis of pregnancy: a review of six national and regional guidelines. Eur J Obstet Gynecol. 2018;231:180–7
6. Abu-Hayyeh S, Papacleovoulou G, Lövgren-Sand- blom A, et al. Intrahepatic cholestasis of pregnancy levels of sulfated progesterone metabolites inhibit farnesoid X receptor resulting in a cholestatic phenotype. Hepatology. 2013;57:716–26.
7. Marschall HU, Wikström Shemer E, et al. Intrahepatic cholestasis of pregnancy and associated hepatobiliary disease: a population-based cohort study. Hepatology. 2013:58;1385-91.
8. Williamson C, Miragoli M, Sheikh Abdul Kadir S, et al. Bile acid signaling in fetal tissues: Implications for intrahepatic cholestasis of preg- nancy. Dig Dis. 2011;29:58–61.
9. Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. Obstet Gynecol. 2014;124:120–33.
10. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World J Gastroenterol. 2009;15:2049–2066.
11. Glantz A, Marschall HU, Mattsson LÅ. Intrahepatic cholestasis of pregnancy: relationships between bile acid levels and fetal complication rates. Hepatology. 2004;40:467–74 .
12. Kong X, Kong Y, Zhang F, et al. Evaluating the effectiveness and safety of ursodeoxycholic acid intreatment of intrahepatic cholestasis of pregnancy:a meta-analysis (a prisma-compliant study). Med (United States). 2016;95:40-9.
13. Kondrackiene J, Beuers U, Kupcinskas L. Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy. Gastroenterology. 2005;129:894-901.
14. Bacq Y, Sentilhes L, Reyes HB, et al. Efficacy of ursodeoxycholic acid in treating intrahepatic cholestasis of pregnancy: a meta-analysis. Gastroenterology. 2012;143:1492–501.
15. Gurung V, Stokes M, Middleton P, et al. Interventions for treating cholestasis in pregnancy. The Cochrane Database of Systematic Reviews 2013;2013(6):CD000493.
16. Grand'Maison S, Durand M, Mahone M. The effects of ursodeoxycholic acid treatment for intrahepatic cholestasis of pregnancy on maternal and fetal outcomes:a meta-analysis including non-randomized studies. J Obstet Gynaecol Canada. 2014;36:632–41.
17. Marschall HU, Wikström Shemer E, Ludvigsson JF, Stephansson O. Intrahepatic cholestasis of pregnancy and associated hepatobiliary disease: a population-based cohort study. Hepatology. 2013;58(4):1385-91.
18. Snape WJ, Shiff S, Cohen S. Effect of deoxycholic acid on colonic motility in the rabbit. Am J Physiol Liver Physiol. 1980;1:321–5.
19. McPherson C, Inder T. Perinatal and neonatal use of sedation and analgesia. Semin Fetal Neonatal Med. 2017;22(5):314-20.
20. Palma J, Reyes H, Ribalta J, et al. Effects of ursodeoxycholic acid in patients with intrahepatic cholestasis of pregnancy. Hepatology. 1992;15:1043–7.
21. Chappell LC, Bell JL, Smith A, et al. Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): randomized controlled trial. Lancet. 2019;394:849–60.
22. Puljic A, Kim E, Page J, et al. The risk of infant and fetal death by each additional week of expectant management in intrahepatic cholestasis of pregnancy by gestational age. Am J Obstet. Gynecol. 2015;212:667. e1–667.e5.
23. Gantt AB, Miller RS. ACOG Committee Opinion. Medically indicated late-preterm and early-term deliveries. Obstet. Gynecol. 2021;138:35-39.