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ORIGINAL ARTICLE

A Systematic Review On Complications of Intrahepatic Cholestasis of Pregnancy

SADIA CHAUDHARY[1], HAFIZ HAFEEZ ANJUM[2], MUHAMMAD USMAN KHAN[3], AMNA KHURRAM[4], UZMA NAZIM[5], MERUB MAQSOOD DAR[6]

[1]*Assistant Professor, Rahbar Medical and Dental College,Lahore.*
[2]*MBBS,FCPS,ESEGH,Senior Registrar ,PGMI.Lahore General Hospital,Lahore.*
[3]*MBBS,FCPS,Senior Registrar,Teaching Hospital,Dera Ghazi Khan,D G Khan.*
[4]*Assistant Professor, Avicenna Medical College,Lahore.*
[5]*Assistant Professor, Rahbar Medical and Dental College,Lahore.*
[6]*Demonstrator, Rahbar Medical and Dental College,Lahore.*
Corresponding author: Sadia Chaudhary, Email: dr.sadiach2000@gmail.com, Cell: 03330440269

ABSTRACT

A potentially dangerous liver condition called intrahepatic cholestasis of pregnancy (ICP) can appear during pregnancy. Primarily manifesting in the third trimester, characteristic symptoms include pruritus (itching) of the soles and palms, elevated blood bile acid levels, and impaired liver function. Several medications have been demonstrated to significantly improve biochemical indicators and gestational age of birth in patients with ICP, and they also alleviate the pruritus experienced by the mother. The use of these drugs during pregnancy may have serious consequences. This systematic review aims to describe maternal and foetal outcomes related to ICP and identify major biochemical and clinical predictors of foetal problems in women diagnosed with ICP. To provide context for the current investigation, Google Scholar and PubMed were searched for articles published between 2012 and 2022. References and bibliographies were employed in manual searches in addition to internet resources. Critical Appraisal Skills Program (CASP) evaluated all selected research papers. Findings were presented using descriptive summary table besides critical analysis. Risks of adverse perinatal outcomes, such as stillbirth and early delivery, were associated with twin pregnancies with ICP. But, premature delivery and neonatal hypoxia are more common in IVF-created twin pregnancies than in naturally conceived twin births. Severe ICP effects are linked with higher risks of stillbirth, admission to a neonatal intensive care unit, and preterm delivery. Some perinatal issues are associated with a mother's serum bile acid levels rising during pregnancy. Congenital disabilities, premature birth, and postpartum bleeding are all associated with ICP. Extreme instances of ICP frequently result in the abrupt and unexpected death of the fetus inside the uterus. ICP and stillbirth develop early in twin pregnancies. Therefore, delivering at 37 weeks may not be desirable. Enhancing fetal prognosis, particularly in twin pregnancies generated through IVF, requires early and correct diagnosis and proper medical intervention. To reduce the likelihood of an indicated preterm delivery, the decision to terminate a pregnancy in pregnancies created through IVF should be made carefully. Despite the fact that there was a clear link between ICP and preeclampsia and GDM, ICP did not raise the risk of stillbirth. Bile acid levels between the mother and fetus correlate, suggesting a causative link between BA levels, prenatal problems, and bad outcomes.

Keywords: Intrahepatic cholestasis of pregnancy; pregnancy outcomes; gynecology; women health

INTRODUCTION

A potentially dangerous liver condition called intrahepatic cholestasis of pregnancy (ICP) can appear during pregnancy (Gardiner et al., 2019). Primarily manifesting in the third trimester, characteristic symptoms include pruritus (itching) of the soles and palms, elevated blood bile acid levels, and impaired liver function (Roy et al., 2021). Shortly after giving birth, both the symptoms and biochemical abnormalities disappear, although they might return with subsequent pregnancies or hormonal birth control. It is often reported by women who have used a combination hormonal contraception and may occur before conception (Çelik et al., 2019). There is substantial evidence linking ICP to an increased risk of negative pregnancy outcomes such as preterm delivery (both spontaneous and induced), foetal distress, amniotic fluid meconium staining, and stillbirth (Fu and Xu, 2021). Pregnancy problems are more likely in women with more severe cholestasis because of an increase in maternal serum bile acid levels (Deniz et al., 2021).

Estimates of ICP prevalence range from 0.2% to 2%, however, this range is very variable across different populations (Liu et al., 2022). The northern hemisphere and South America are the primary regions of occurrence. Women with many pregnancies, those whose pregnancies were generated through in vitro fertilisation, and women over 35 are more likely to experience ICP (Gök et al., 2022b). Higher rates of cholelithiasis and hepatitis C seropositivity were found in women with ICP in an investigation. ICP has a complicated aetiology, but it appears to be connected to the cholestatic impact of reproductive hormones in females who are predisposed to developing the disorder (Al-Obaidly et al., 2021). Familial clustering of ICP cases and reports of pedigrees in which inheritance follows a sex-restricted, dominant pattern provide evidence of genetic vulnerability to the illness. Genes for biliary transport proteins and the farnesoid X receptor have both been found to contain genetic variation (Aftab et al., 2021). The reproductive hormones may have a role in the development of ICP, as shown by the disease's natural history and by studies in which oral progesterone was used to avert premature labour (Chappell et al., 2020). Estrogen has been shown in rodent studies to contribute to cholestasis development by decreasing the hepatic biliary transport protein's expression and by triggering the internalisation of the bile salt export pump and bile acid transporter (Mei et al., 2019). The aetiology of ICP is said to be influenced by several environmental variables, including dietary selenium levels. Additionally, vitamin D insufficiency has been linked to ICP in women, and this is a period when levels are likely to be lower. The harmful effects of toxic bile acids that build up in the foetal compartment, are most likely the cause of the foetal problems (Ozel et al., 2020).

Ursodeoxycholic acid, a standard treatment for ICP, has been proven to be beneficial in easing maternal symptoms and lowering blood bile acid levels (Ovadia et al., 2021). However, there are not any sufficiently large randomised controlled trials to determine if ursodeoxycholic acid lowers the risk of unfavourable perinatal outcomes (Sitaula et al., 2021). Numerous studies support active treatment techniques that include prenatal monitoring that is intensified and intentional early deliveries (Mitra et al., 2020; Shafqat et al., 2022). Although there is little body of research to support these procedures, doctors must decide if the risks of an early birth exceed those of prolonging a pregnancy plagued by intrahepatic cholestasis (Parihar and Singh, 2019). Although not completely understood, the pathophysiology of ICP is likely to include several factors, including the environment, genes, and hormones. ICP is generally harmless to women, but there have been reports that it has significant prenatal consequences (Di

Mascio et al., 2021). ICP has been linked to a higher risk of premature birth, meconium stains in amniotic fluid, bradycardia in the foetus, foetal discomfort, and foetal death. The primary causes of poor foetal outcomes and their contributing factors remain mostly unknown (Smith and Rood, 2020). It has been demonstrated that increased maternal total serum bile acids (>40 micromol/L) during pregnancy are linked to adverse foetal outcomes, such as asphyxial episodes and spontaneous premature birth. However, it has not been consistently possible to identify precise predictors of pregnancy outcomes (Chappell et al., 2019).

Ursodeoxycholic acid is a tertiary bile acid found in small concentrations in normal human serum and used to treat ICP (Gök et al., 2022a). Though it is not approved for use during pregnancy, it treats intrahepatic pregnancy cholestasis. Case reports and limited studies suggest it may assist some pregnant women (Arora et al., 2021). Women with intrahepatic cholestasis of pregnancy who took ursodeoxycholic acid had a statistically significant decrease in pruritus compared to those who took a placebo, according to the biggest randomised controlled trial of the drug (Walker et al., 2020). In addition, serum bile acid levels were unaffected by ursodeoxycholic acid administration, whereas ALT, bilirubin, and GGT were all reduced. Twelve percent of patients had elevated ALT but normal blood bile acids, and sixty-three percent had moderate cholestasis with serum bile acid levels. It may be partly due to the diagnostic criteria utilised (Sharma et al., 2018).

However, evidence for a potential benefit of ursodeoxycholic acid on foetal outcomes remained unclear, and more research is warranted. Many modest studies have suggested that intrahepatic cholestasis of pregnancy treatment approaches, including medication with ursodeoxycholic acid, enhance outcomes (Gao et al., 2020). Ursodeoxycholic acid dosage is normally between 500 mg and 2 g/d and is titrated according to symptoms (Liu et al., 2018). Nausea, vomiting, or loose stools were the most frequently reported adverse events in recent placebo-controlled research (Kong et al., 2021), occurring in 16% of the ursodeoxycholic acid arm and 9% of the placebo arm, respectively. No adverse impacts on the developing baby are visible. Although the exact mechanism of action is unclear, research has indicated that therapy decreases total serum bile acids in both umbilical and maternal cord serum. Treatment with ursodeoxycholic acid not only improves placental form and function, but also decreases bile acid levels (AHUJA et al., 2021). The aforementioned medications have been demonstrated to significantly improve biochemical indicators and gestational age of birth in patients with ICP, and they also alleviate the pruritus experienced by the mother. The use of these drugs during pregnancy may have serious consequences. The purpose of this systematic review is to provide a description of maternal and foetal outcomes related with ICP and to identify major biochemical and clinical predictors of foetal problems in women diagnosed with ICP.

MATERIAL AND METHODS

Search strategy: The review's search strategy is crucially important. Most papers are retrieved for researchers to assess whether or not they match inclusion/exclusion criteria. The entities and data used in the search impact the search's quality. In light of this, it is essential to find all pertinent research and consider them in the review. This evaluation used abstract and title-related phrases and the usual keyword searches to locate pertinent references. Utilizing search phrases consistently made it easier to confirm that the information provided was accurate and valuable. We searched through the book and journal databases and the library's internet databases for this investigation. We used both online and offline techniques to find academic literature. Journals, conferences, and their abstracts are all carefully screened when doing a hand search.

Information Sources: To provide context for the current investigation, Google Scholar and PubMed were searched for articles published between 2012 and 2022. There are different names for manual search techniques like the snowball method. References and bibliographies were employed in manual searches in addition to internet resources. We utilised a variety of search terms to locate trustworthy sites. On topic header and keyword combinations, a Boolean test was run.

Quality Assessment: With the help of the Critical Appraisal Skills Program (CASP), some research were evaluated. A rigorous review procedure is needed to determine which articles are most pertinent for future investigation. Ten particular issues are addressed to assess a research paper's quality. By employing methods relevant to the study and taking ethical issues into account while answering checklist questions, the researchers appear to have succeeded in achieving their objectives. Because of its simplicity and dependability, the Cochrane Collaboration and the World Health Organization both recommend using the CASP method to synthesise qualitative evidence. The CASP score has been proved to be a reliable indicator of how transparent researchers' methods and conclusions are (McGill et al., 2021). The CASP tool was found to provide inferior reviewer agreement when compared to other evaluation methods (Strijker et al., 2020). The ETQS and the JBI were compared to the CASP tool utilising Hannes et alfive .'s validity criteria (Skarbek, 2020). In terms of its theoretical and methodological soundness and interpretive and evaluative validity, the CASP instrument was judged to be the most accurate of the three. For the synthesis of qualitative data, the CASP tool is without a doubt the industry standard for checklist- and criteria-based quality evaluation in the sectors of health and social care (Harris et al., 2019). to be appropriate for the research's objectives and the current investigation's character. A researcher's questions about reflexivity are a trustworthy sign of the calibre of their work. To ensure the validity of the findings and guard against bias in the research, it is essential to address all raised issues.

Data Extraction and Synthesis of results: Complete articles and abstracts were assessed for their relevancy to the review's objectives, and those that did not satisfy those standards were ignored. To assist you in analysing each argument, a comprehensive list of reliable references has been compiled. A selection of published papers was reviewed by academics using a methodical approach to data collecting. Authors, publication date, research stage, and the kinds and quantities of medical cases are only a few of the study's characteristics. The sources themselves are supplied, and any potential biases are mentioned. Findings were presented using a descriptive summary table besides critical analysis.

RESULTS

Studies Selection: A literature search may turn up a massive amount of results, but only a fraction of them would be suitable for inclusion in the review (Liamputtong, 2019). Studies were evaluated for eligibility based on the inclusion and exclusion criteria established for this analysis. One technique for locating applicable research was reading abstracts and seriously considering their potential relevance and application. Articles were chosen after their abstracts were reviewed in order to see if they will present any new or interesting research. 10,276 studies were first scoured via various databases. A total of 5,845 research had to be thrown out because they were duplicates. After filtering out 1,792 results, we were left with 2,639 hits from our search of article titles, abstracts, keywords, and full texts where available. According to the review of the referenced studies, 1,716 were disregarded. We eliminated 913 studies because they had flawed study designs, leaving 10 publications. PRISMA has diagrammed the entire procedure in figure 1.

Descriptive Outcomes: In X. Liu et al., (2016), three significant findings were revealed: i.e., (1) Preterm birth, stillbirth, and other adverse perinatal outcomes were substantially increased by ICP, (2) stillbirths occurred in twin gestation at 33–35 gestational weeks, and (3) women carrying twins who had severe ICP were most at

risk for these outcomes. In this population, smoking and alcohol consumption were extremely rare (0.3%). In addition to being slightly older and less obese, women with ICP were also more probable to be primiparous and use assisted reproduction. Preeclampsia and GDM occurred more frequently in the ICP group. These five twin pregnancies were all dichorionic in the placenta. In twin pregnancies, ICP was linked to a higher risk of stillbirth. Spontaneous preterm births mostly caused the greater percentage of preterm births in the ICP group. The higher risk for stillbirth among ICP patients was still present after adjusting for preeclampsia.

In Feng et al., (2018), IVF-created twin pregnancies had a greater incidence of ICP than spontaneously conceived twin pregnancies (9.88% vs. 4.58%). IVF was discovered to be the main contributing cause to early-onset ICP. Additionally, the IVF group had a higher prevalence of ICP-related clinical signs than the SC group, including skin itching, skin scratching, and jaundice. Neonatal asphyxia and preterm birth were more common in the IVF group comparitively. When corrected for preterm birth, chorionicity, and early-onset ICP, twin pregnancies had an OR of 45.84, which was more frequently linked with newborn hypoxia. Though the fetal distress incidence tended to be higher in the IVF group, there were no appreciable changes in cesarean section rates, stillbirths, or meconium staining between the two groups. While TBA or CG rose, there was a rising trend in the prevalence of newborn problems. However, the relationship between newborn problems and TBA levels did not reach statistical significance ($P > 0.05$).

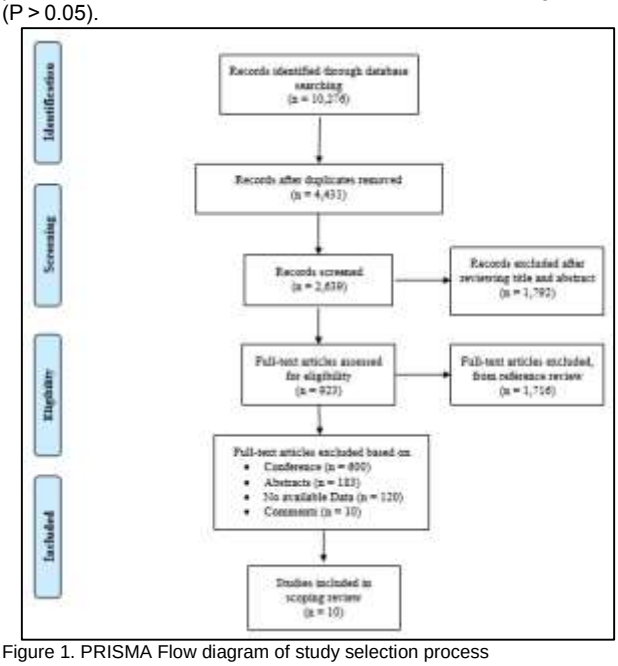

Figure 1. PRISMA Flow diagram of study selection process

Table 1: Summary of the included studies for the systematic review.

Authors& Year	Aims	Research Design and CASP Score	Sample	Results	Conclusion
(Liu et al., 2016)	To characterize the perinatal results of twin pregnancies affected by intrahepatic cholestasis of pregnancy	Retrospective cohort study (9/10)	1922 twin and 92273 singleton pregnancies	Twin pregnancies had a higher incidence of stillbirth (3.9% and 0.8% in the ICP and non-ICP groups, respectively). Twins and ICP stillbirths happened between weeks 33 and 35 of pregnancy, whereas singletons happened between weeks 36 and 38. ICP was linked to a higher risk of preterm delivery (births that occur before 37 weeks) in twins.	ICP greatly increases the odds of severe perinatal outcomes, such as stillbirth and premature delivery, in twin pregnancies. Twin gestation has an earlier stillbirth rate than singleton gestation, indicating that these mothers may think about having an earlier planned delivery.
(Feng et al., 2018)	To investigate how in vitro fertilization-embryo transfer (IVF-ET) affected the perinatal results of ICP in twin pregnancies.	Retrospective analysis (10/10)	142 twin pregnant women	The IVF group had a greater frequency of early-onset ICP ($P = 0.015$) and more frequent clinical symptoms ($P = 0.020$), such as skin itching, skin scratching, and jaundice, compared to the spontaneous conception (SC) group. In addition, compared to the SC group, the IVF group experienced increased incidence of preterm birth and neonatal hypoxia.	The group of twin pregnancies created by IVF had a greater probability of developing early-onset ICP, as well as clinical symptoms and worse perinatal outcomes.
(Liu et al., 2020)	Investigating the links between ICP and preeclampsia, GDM, and unfavorable maternal and neonatal consequences of ICP were also goals of the study.	Retrospective cohort study (9/10)	95,728 singleton pregnancies who delivered in 14 representative hospitals	ICP was linked to GDM and preeclampsia in women. ICP women had more planned and labor cesareans. ICP increases the risk of iatrogenic preterm birth and neonatal critical care unit hospitalization. ICP instances had no increased stillbirth risk.	In singleton pregnancies, ICP was linked to GDM and preeclampsia. ICP increases the likelihood of unfavorable perinatal outcomes.
(Rook et al., 2012)	To examine fetal outcomes in pregnancies complicated by ICP	Cohort study (9/10)	101 women diagnosed with ICP	33% of births were complicated, mostly by respiratory distress. TBA levels over 100 mol/L were associated with 3 out of 5 fetal problems. ICP in prior pregnancies reduced fetal problems.	Elevated TBA and other maternal clinical and laboratory characteristics did not seem to be significant predictors of fetal problems in ICP.
(Brouwers et al., 2015)	To examine the relationship between the success of an ICP-affected pregnancy and bile acid (BA) levels.	Retrospective study (9/10)	215 women with pruritus and bile acid (BA) levels ≥10 μmol/L	Severe ICP cases had considerably higher rates of spontaneous preterm birth (19.0%), meconium-stained fluid (47.6%), and neonatal mortality (9.5%). Increased BA levels were substantially linked to meconium-stained amniotic fluid, spontaneous preterm delivery, and perinatal deaths. Umbilical cord blood BA levels and maternal BA levels at diagnosis and delivery showed a favorable correlation.	ICP severity is linked to poor pregnancy outcomes. BA levels in the mother and fetus are correlated.
(Geenes et al., 2014)	To examine the pregnancy complications linked with severe ICP.	Prospective population-based case-control study	Control data of over 1.2 million cases	Preterm birth, stillbirth, and hospitalization to a neonatal unit were the primary outcome indicators examined. An estimated incidence of 9.2 occurrences per 10,000 births was determined based on the identification of 713 confirmed cases with severe ICP.	Perinatal complications, such as stillbirth, were more likely to occur.
(Madazli et al., 2015)	To identify clinical and biochemical indicators of fetal problems as well as maternal and fetal features related to ICP.	Retrospective study (9/10)	89 singleton pregnancies with ICP	Patients who were identified before 30 weeks of gestation had considerably greater rates of respiratory distress syndrome (RDS), fetal growth restriction, fetal distress, and preterm birth than those who received a diagnosis after 34 weeks.	In individuals with ICP, gestational age at diagnosis is a significant independent factor for predicting poor perinatal outcomes.

(Batsry et al., 2019)	To compare twin and singleton intrahepatic cholestasis of pregnancy problems.	Retrospective cohort study (8/10)	56 twin pregnancies and 186 singleton pregnancies	ICP was found sooner in twin pregnancies (33.1 vs. 35.1) Twin pregnancies had greater total bile acid levels than singletons. No pregnancy had fetal death. Both groups had similar 5-minute Apgar scores and umbilical artery and vein PH at birth.	With an earlier onset and larger levels of maternal blood total bile acids, ICP in twin pregnancies were severe than in singleton pregnancies.
(Mei et al., 2018)	To look into perinatal outcomes in monochorionic diamniotic (MCDA) twin pregnancies in ICP.	Retrospective observational study (10/10)	58 women with ICP	Incidences of iatrogenic preterm birth and gestational diabetes mellitus (GDM) significantly greater in the severe ICP group than in the moderate ICP group.	GA at diagnosis of ICP less than 32 weeks and TBA higher than 40umol/L are linked to poor perinatal outcomes for mothers carrying twins with ICP and MCDA.
(Arthuis et al., 2020)	To compare the neonatal and maternal effects of ICP-affected and unaffected pregnancies.	Case-control study	140 women with ICP and 560 normal controls	140 mothers with cholestasis and 560 controls had no fetal fatalities. Neonatal RDS was more common in women with intrahepatic cholestasis. This risk remained after adjusting for delivery mode and gestational age. Case mothers had double the postpartum hemorrhage rate.	The newborns in the cholestasis group had greater rates of neonatal morbidity and respiratory distress syndrome.

In C. Liu et al., (2020), in the ICP group, the prevalence of GDM was noticeably higher. The preeclampsia incidence was also markedly higher in the ICP group as compared to the group without ICP. Women with ICP who developed preeclampsia had no discernible variations in maternal age or nulliparous status from those who did not. Preeclampsia cases in women with ICP who were overweight and had a greater percentage of assisted conceptions were both significantly higher. Women in the ICP group had greater rates of SGA (3.5% vs. 2.0%), earlier pregnancies and lower birth weights. However, these differences were no longer statistically significant after adjusting for the confounding variables. The rates of iatrogenic preterm delivery and planned cesarean deliveries (74.3% vs. 43.7%) were all substantially higher in the ICP group with P=0.020.

In Brouwers et al., (2015), the percentage of infants born short for gestational age (SGA) did not vary (p=0.831), but birth weight was considerably lower in the more severe ICP instances (p=0.009). With increased ICP severity, spontaneous preterm birth was more prevalent (p=0.023). Additionally, the more severe cases were more likely to have meconium-stained amniotic fluid (p=0.003). 7.4% of all patients had a postpartum haemorrhage, with the moderate group having the greatest prevalence (p=0.019). During the investigation, asphyxia was seen in two patients, both of which belonged to the moderate ICP group. Perinatal deaths occurred in two cases (0.9%) in the population under study. 9.5% of the severe ICP cases—both intrauterine deaths were identified in the group with severe ICP (p=0.009).

In Geenes et al., (2014), ICP patients gave birth earlier than control mothers. Preterm births that were both spontaneous and iatrogenic increased significantly. With 17% of preterm births in the ICP group and 2.7% in the controls being induced or chosen, iatrogenic causes account for the bulk of preterm births. In the ICP population, there were appreciably more stillbirths and a greater chance of being admitted to the newborn ICU. Preterm birth (46%) and respiratory issues (31%) were cited as the major causes for admission to the newborn unit. Prelabor decelerations or variable decelerations (49.1%), bradycardia (8.6%), tachycardia (6.7%), and early decelerations (10.3%) were the most frequently reported abnormalities. Compared to controls, women with significant ICP and singleton pregnancies (n = 669) had higher odds of preterm delivery, neonatal unit hospitalization, and stillbirth. Coexisting pregnancy problems were linked to seven out of ten stillbirths in ICP instances. Significant correlations have been discovered between the bile acid level in maternal serum and meconium-stained amniotic fluid, spontaneous preterm labor, stillbirth, and premature birth.

In Madazli et al., (2015), Patients who were diagnosed before 30 weeks of gestation had a substantially greater incidence of fetal distress, fetal growth restriction, respiratory distress syndrome (RDS), and delivery before 37 weeks (p 0.01). Fetal growth restriction, RDS, preterm birth, and fetal distress rates did not change substantially from TBA subgroups (p>0.05). Gestational age (GA) upon ICP diagnosis is a risk factor by itself for GA at 35 weeks and for a composite unfavorable newborn outcome, according to Mei et al. (2018). Only 18 patients underwent the whole course of blood testing, and of them, 17 patients' TBA levels were fallen following therapy, 6 had amniotic fluid that was stained with meconium, and 1 had experienced severe hypoxia.

In Batsry et al., (2019), when compared to singleton pregnancies, twin pregnancies resulted in earlier deliveries (35.4 vs. 37.5). Most births in both groups were iatrogenic, especially caused by ICP in 82.7% of singleton deliveries and 55.4% of twin deliveries (P=0.001). Twins had iatrogenic preterm birth more frequently than singletons for both preterm births of 37 weeks and 35 weeks. These significant differences not continue to be statistically significant after correction. In our group, there were no pregnancies complicated by fetal death. Preeclampsia and gestational diabetes mellitus rates did not substantially differ between the two groups, however. Indicating ICP as a further factor contributing to the greater prevalence of preterm delivery in singleton vs twin gestations, there was higher rate of iatrogenic preterm birth because of ICP among twins than those of singletons. However, in terms of newborn outcomes, both groups were comparable.

In Arthuis et al., (2020), compared to controls, neonates exposed to cholestasis had a higher chance of developing an RDS. In the cholestasis group compared to the control group, the rate of admission to neonatal critical care units was around three times greater (P = 0.018). In addition, cholestasis patients had greater infant morbidity than controls. Induction of labor was achieved by active obstetric treatment in 82.1% of case women and 18.4% of the control group. Between the groups, there was no difference in the cesarean rate during childbirth (P = 0.457). Contrarily, the case women experienced a higher rate of planned (prelabor) cesareans (12% versus 2%, P 0.001). In the case group, postpartum hemorrhages occurred 25% more frequently except maternal blood transfusions (P = 0.002).

DISCUSSION

With technology's development over 30 years ago, safety issues for mother and fetus have been a worry. A large portion of the danger is attributable to the rise in multiple gestations that has increased risks for perinatal morbidity and preterm death. It is generally recognized that singleton pregnancies with ICP have an elevated risk of unexpected fetal death. The mechanism of fetal mortality can be related to bile acid-related cardiac arrhythmia. It is also possible that bile acids might also produce noticeably constricted chorionic arteries in the placenta, which could result in acute anoxia and rapid death. Late in pregnancy, when contractions may damage restricted placental chorionic arteries, the risk of fetal death appears to be highest (Luo et al., 2021). Deliveries are typically carried out at or near term due to the unexpected and late start nature of fetal mortality in singleton pregnancies with ICP. The correlation between moderate ICP and fetal demise has been historical as a result of fetal monitoring tools and actively managed policies (Çelik and Çalışkan, 2021), however high ICP continues to be linked to an elevated risk of fetal demise in singleton pregnancies (Alemdaroğlu et al., 2021). Since bile acid may boost myometrium reactivity to the effects of oxytocin, ICP is linked to higher risks of spontaneous preterm labor (Arafa and Dong, 2020). Women with ICP have been found to have higher incidences of preeclampsia and gestational diabetes

(Vasavan et al., 2021). Preeclampsia and ICP are both conditions that only occur during pregnancy, and they have several clinical characteristics, such as a greater frequency in multifetal pregnancies.

Later investigations revealed relative risks (Aydın et al., 2020; Shen et al., 2019; ul Hassan et al., 2022). However, several studies revealed divergent findings. Pregnancies produced with reproductive technologies and instinctively occurring conceptions have similar perinatal outcomes (Triunfo et al., 2022). Birth weight, Apgar score, or illnesses associated with pregnancy were not associated with IVF/ICSI conception (Aydın et al., 2020). Early ICP onset had poor clinical symptoms (higher incidence of meconium staining, fetal distress, premature delivery, cesarean section, and newborn asphyxia) than late-onset ICP, as well as higher TBIL, TBA, bilirubin concentrations, and aminotransferase activity (Al-Obaidly et al., 2019). Clinical signs with a twin pregnancy might be more severe (Saad et al., 2021). The relative risk of preterm birth was 1.07 in the IVF group, according to a previous comprehensive study that found preterm twins differed greatly in premature delivery. Preterm delivery was independently predicted by the early start of increased serum bile acid (Wood et al., 2018).

Uncertain processes underlie the fetal problems in ICP, although they seem to be related to the impact of excessive bile acid concentrations in the fetal compartment. A dose-dependent bile acid impact on myometrial contractility may be responsible for spontaneous preterm labor (Herrera et al., 2018). All pregnant lambs given cholic acid had meconium-stained amniotic fluid but no other evidence of fetal distress (Lagon et al., 2022). Studies on rabbits receiving intratracheal injections of bile acids show that these injections cause eosinophilic infiltration, atelectasis, and the hyaline membrane formation (Huang et al., 2022). These studies provide evidence that bile acids are involved in the cause of neonatal respiratory distress. Interestingly, a recent group of children with unanticipated respiratory distress in addition to ICP reported improved health after receiving intratracheal surfactant therapy (Roediger and Fleckenstein, 2021).

An increase in intestinal motility and subsequent meconium passing as a result of bile acids may be responsible for gestational diabetes mellitus (Asali et al., 2021). The higher prevalence of RDS associated with ICP is assumed to be caused by bile acid aspiration (Palmer et al., 2019). There are presently two major hypotheses for the pathophysiology of fetal mortality in ICP: either a fast onset of fetal arrhythmia (Sarker et al., 2022) which is considered to be brought on by high bile acid concentrations. As predicted by other investigation, there were more women with diabetes among ICP patients compared to controls (Lindor et al., 2019). While confounding variables are unclear, this connection may increase stillbirth rates (Di Mascio et al., 2021). When serum bile acid concentrations are at least 100 mol/L, it also rises with BA level (Walker et al., 2020). The catastrophic incidents recorded in this context demonstrate that bile acids are not a foolproof monitoring marker and that the amount might rise suddenly (Sharma et al., 2018).

CONCLUSION

We found that twin pregnancies with ICP had considerably higher chances of negative perinatal outcomes, such as stillbirth and premature delivery. ICP and stillbirth develop early in twin pregnancies; therefore delivering at 37 weeks may not be desirable. Compared to spontaneously produced twin pregnancies, IVF-created twin pregnancies are more likely to experience poor fetal outcomes, including preterm birth and neonatal hypoxia. Therefore, enhancing fetal prognosis, particularly in twin pregnancies generated through IVF, requires early and correct diagnosis, and proper medical intervention. A higher risk of stillbirth, neonatal unit hospitalization, and premature delivery is linked to severe ICP effects. Increasing levels of maternal serum bile acids are linked with higher risks of certain perinatal problems. The decision to terminate a pregnancy in pregnancies created through IVF should be made carefully to reduce the likelihood of an indicated preterm delivery. ICP is linked to perinatal mortality, meconium-stained amniotic fluid, spontaneous preterm birth, and postpartum haemorrhage. Intrauterine death that occurs suddenly and unexpectedly is common in severe ICP cases. Bile acid levels between the mother and fetus correlate, suggesting a causative link between BA levels, prenatal problems, and bad outcomes.

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