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FETAL PROGNOSIS IN INTRAHEPATIC CHOLESTASIS OF PREGNANCY

D.A. MEREȚ[1] L.M. ROGOZEA[1] M. IRIMIE[1]
M.A. MOGA[1] M.A. DINUȚĂ-SMEU[1] A. PRAHOVEANU[1]

Abstract: *Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-specific liver disease, characterized by pruritus associated with elevated serum bile acid concentrations and abnormal liver function tests in the absence of another obvious etiology. Although maternal symptoms are, in most cases, self-limited and resolve rapidly after delivery, clinical and scientific interest in this entity derives from its disproportionate impact on fetal prognosis, making ICP a condition of major clinical relevance in maternal-fetal medicine: PubMed, Embase, and Cochrane Library, complemented by an additional literature exploration through Google Scholar to identify relevant articles that were not indexed in a standard way The methodological quality of the included studies was assessed by evaluating study design, sample size, inclusion criteria, and potential sources of bias, including selection, confounding, and reporting bias. Maternal disease severity may appear disproportionate to the potential fetal consequences, making clinical management complex and highly individualized. Conclusion. This review highlights the current evidence linking ICP to adverse perinatal outcomes, with important implications for risk stratification and clinical management practice.*

Keywords: *intrahepatic cholestasis of pregnancy, maternal-fetal medicine, perinatal outcomes, bile acids, liver function tests*

1. Introduction

Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-specific liver disease, characterized by pruritus associated with elevated serum bile acid concentrations and abnormal liver function tests in the absence of another obvious etiology [1]. Although maternal symptoms are, in most cases, self-limited and resolve rapidly after delivery, clinical and scientific interest in this entity derives from its disproportionate impact on fetal prognosis, making ICP a pathology of major relevance in maternal-fetal medicine [2].

The incidence of ICP varies considerably across populations worldwide, estimated to be between 0.2% and 2% in European populations, but reaching significantly higher values in certain ethnic groups,

[1] Faculty of Medicine, *Transilvania* University of Braşov

such as South American or Scandinavian populations, suggesting an important role for genetic and environmental factors in disease pathogenesis [3,4]. This epidemiological variability reflects the complexity of the mechanisms involved, including mutations in bile acid transporter genes (ABCB4, ABCB11), hormonal influences, and epigenetic factors that modulate the hepatic response to pregnancy [5].

From a pathophysiological point of view, ICP is defined by a disturbance in bile acid that causes systemic effects and, in particular adverse effects within the fetoplacental compartment. Bile acids are not only biochemical markers of the disease, but also biologically active agents, capable of crossing the placental barrier and inducing functional and structural changes at the fetal level, including cardiac dysfunction, oxidative stress, and alteration of placental flow [6,7].

Over the past two decades, the concept that ICP severity, measured by serum bile acid levels, is directly correlated with the risk of adverse fetal events has become well established. Large cohort studies have demonstrated that values ≥40 µmol/L are associated with a significantly higher risk of preterm birth, meconium-stained amniotic fluid and fetal distress, while levels ≥100 µmol/L define a high-risk category of intrauterine fetal death [8,9]. However, the relationship between maternal biomarkers and fetal development is not always linear, suggesting the existence of additional mechanisms involved in fetal vulnerability.

A distinctive feature of ICP is the unpredictable nature of fetal complications. Unlike other obstetric pathologies in which fetal deterioration is progressive and detectable by standard monitoring methods, in ICP fetal death can occur suddenly, in the absence of obvious premonitory signs, which limits the effectiveness of conventional antenatal surveillance strategies [10]. This peculiarity suggests the involvement of acute mechanisms, possibly of an arrhythmic or metabolic nature, induced by exposure to elevated bile acid concentrations.

In this context, the clinical management of ICP remains a major challenge, requiring the balance between the risk of iatrogenic prematurity and that of intrauterine fetal death. Decisions about optimal timing of delivery are currently mainly guided by bile acid levels and gestational age, but the lack of reliable predictive markers for acute events limits the precision of these strategies [11].

Therefore, a deep understanding of the mechanisms underlying the fetal prognosis in ICP, as well as the integration of recent epidemiological and clinical data, are essential to optimise the therapeutic approach. The present review aims to critically analyses systematic the current evidence on the relationship between ICP and perinatal outcomes, with a focus on pathophysiological mechanisms, risk factors, and clinical implications relevant to medical practice [12,13].

2. Material and Methods

2.1. Study design

This article was designed as a structured narrative review informed by PRISMA methodological principles, to improve transparency in study selection and reporting. The methodological approach aimed to combine the rigor of a systematic review with the analytical flexibility of a narrative review, allowing a

critical and contextualized interpretation of the data on fetal prognosis in ICP.

2.2. Search strategy

A systematic literature search was conducted in the major international databases PubMed, Embase, and the Cochrane Library, supplemented by a Google Scholar search to identify relevant articles not captured by the primary database search.

The search strategy combined MeSH terms and free-text keywords, such as "intrahepatic cholestasis of pregnancy", "fetal prognosis", "bile acids", "stillbirth", "preterm birth", "fetal distress", "perinatal outcomes". Boolean operators "AND" and "OR" were used to optimize the sensitivity and specificity of the search. The time range was limited to the period 2010–2025, to reflect recent developments in understanding the mechanisms and management of ICP, without excluding relevant fundamental studies prior to this period.

2.3. Inclusion and exclusion criteria

The selection of studies was carried out based on predefined criteria.

Inclusion criteria

The following studies were included:

- observational studies (cohort, case-control) that evaluated the relationship between ICP and fetal outcomes;
- prospective and retrospective studies that reported bile acid levels and their correlation with perinatal complications;
- meta-analyses and systematic reviews relevant to pathophysiological mechanisms and risk stratification;
- articles published in English in peer-reviewed journals.

Exclusion criteria

The following were excluded:

- case reports and small case series (<30 patients);
- articles without access to the full text;
- studies that did not clearly differentiate ICP from other hepatic or obstetric pathologies;
- studies with a high risk of bias or insufficient data for critical interpretation.

2.4. Study selection process

The selection process was carried out in several stages, according to the PRISMA recommendations:

1. *Identification* - extraction of items from databases and removal of duplicates;
2. *Screening* – evaluating titles and abstracts for relevance;
3. *Eligibility* – full text analysis of potentially relevant studies;
4. *Inclusion* – the final selection of studies that met the methodological criteria.

The process was summarized through a PRISMA flow chart, highlighting the selection path and the reasons for excluding the studies.

2.5. Data extraction and analysis

The following variables were systematically extracted from the included studies:

- characteristics of the population studied (size, geographical distribution);

- diagnostic criteria for ICP;
- serum bile acid levels;
- fetal outcomes (preterm birth, meconium-stained amniotic fluid, fetal distress, intrauterine fetal death);
- management strategies and therapeutic interventions.

Data analysis was performed through a critical narrative synthesis, given the heterogeneity of the included studies, which limited the possibility of a quantitative meta-analysis. The emphasis was placed on identifying recurring patterns, probable causal relationships, and discrepancies between studies.

Assessment of the quality of studies

The methodological quality of the included studies was assessed by analysing the design, sample size, inclusion criteria, and potential sources of bias (selection, confounding, reporting). Studies with a high risk of bias were interpreted with caution and used primarily for contextual discussion.

Ethical considerations

As this was a review study, approval from the ethics committee was not required. However, the principles of academic integrity and good citation practices were respected, avoiding unjustified reproduction of content and ensuring the originality of the presented synthesis.

3. Results

3.1. CORRELATION BETWEEN BILE ACIDS AND FETAL RISK: CLINICAL EVIDENCE

In ICP, the relationship between maternal bile acid levels and fetal outcome represents the conceptual core of the entire clinical approach [14,15]. During the past two decades, the accumulation of data from large observational studies has allowed the outline of a consistent link between the severity of maternal biochemical imbalance and the risk of adverse perinatal events [16-18]. However, this relationship is not simple or linear but reflects the interaction between fetal exposure to bile acids, its duration, and the capacity of the fetoplacental unit to compensate for the metabolic insult [19-23].

A landmark in the literature is the extensive analysis by Ovadia et al., which integrated data from multiple cohorts and demonstrated that the risk of fetal complications increases progressively with maternal serum bile acid levels [24]. This observation has allowed the definition of the risk thresholds currently used in clinical practice. Thus, values below 40 µmol/L are generally associated with a relatively low risk of serious events, while exceeding this level marks the transition to a high-risk zone, characterized by a higher incidence of premature birth, fetal distress, and the presence of meconium in the amniotic fluid. At values greater than 100 µmol/L, the risk of intrauterine fetal death becomes significant, suggesting the existence of a biological threshold above which the fetal adaptation mechanisms are exceeded.

Preterm birth is the most common clinical consequence associated with ICP and is reported with considerably higher frequency than in the general population. It occurs both spontaneously, probably through direct effects of bile acids on uterine contractility and prostaglandin metabolism, and iatrogenic ally, because of a medical decision to terminate a

pregnancy early for prophylactic purposes. This dual determination complicates the interpretation of the causal relationship, but most of the data suggest that elevated levels of bile acid contribute directly to the onset of preterm labor [25,26].

Another clinically relevant feature is the increased frequency of meconium-stained amniotic fluid, which occurs more frequently in pregnancies complicated by cholestasis. The presence of meconium is considered an indirect indicator of fetal distress and likely reflects the stimulatory effects of bile acids on fetal intestinal motility and anal sphincter tone. In parallel, acute fetal distress, manifested by cardiotocographic changes, is more frequently observed in these cases, although the correlation between these changes and severe events remains inconsistent, highlighting the limitations of conventional monitoring [27,28].

The most severe consequence of ICP is intrauterine fetal death, a rare but profoundly unpredictable event. Unlike other obstetric pathologies, in which fetal deterioration is progressive and detectable by standard methods, in this context fetal death can occur suddenly, without obvious premonitory signs. The available data suggest that this risk increases with gestational age, especially after 36 weeks, and is closely correlated with elevated bile acid levels [24,29]. The absence of prior changes in fetal growth or Doppler flow patterns supports the hypothesis of an acute mechanism, probably of an arrhythmic or metabolic nature, rather than a chronic hypoxic process.

Although bile acids are the main marker used in risk assessment, clinical experience and data from the literature indicate that they cannot fully explain the variability in fetal development. There are situations in which complications occur at moderate levels, as well as cases in which pregnancies develop favourably despite elevated concentrations. This heterogeneity suggests the involvement of additional factors, such as fetal genetic susceptibility, the efficiency of placental transport and detoxification mechanisms, and the duration of exposure to bile acids [30].

Consequently, the relationship between bile acids and fetal prognosis must be interpreted in a broader framework that integrates not only the absolute values of biomarkers but also the individual clinical context. This perspective is essential for optimizing therapeutic decisions, especially with respect to the timing of delivery, where the balance between the risk of prematurity and fetal death remains delicate and often difficult to establish.

3.2. CLINICAL MANAGEMENT AND TIMING OF BIRTH IN INTRAHEPATIC CHOLESTASIS OF PREGNANCY

The management of ICP is at the intersection of preventing severe fetal complications and avoiding the consequences of iatrogenic prematurity, which transforms the therapeutic approach into a complex and individualized decision-making process.

The particularity of this condition lies in the discrepancy between maternal evolution, generally benign and self-limited, and the potentially severe impact on the fetus, determined by exposure to bile acids in elevated concentrations. For this reason, management is primarily directed toward reducing fetal risk, and delivery remains the only intervention

with a definitive effect on removing intrauterine exposure [31,32].

In clinical practice, treatment is primarily based on serum bile acid levels and gestational age, which are the pillars of risk stratification. This approach is derived from data that indicate a correlation between the severity of cholestasis and the likelihood of fetal complications, but the variability of the clinical response requires a contextualized interpretation of each case [32]. Thus, ICP is considered a spectrum of severity and therapeutic decisions tailored to the individual, depending on the dynamics of biochemical parameters and the obstetric context.

Maternal monitoring is essential and is based on repeated evaluation of bile acids and liver function tests. Serial determinations are particularly important because bile acid levels can increase rapidly, especially in the third trimester, and a moderate initial value does not exclude the evolution to severe forms [33]. In parallel, monitoring of transaminases, bilirubin, and coagulation parameters allows the identification of hepatic complications and possible associated disorders. The dynamics of these parameters provides more relevant information than an isolated determination and contributes to the adjustment of therapeutic conduct [34].

An important aspect of interpreting the results is the variability of bile acid values depending on the time of collection. Postprandial values are often higher than those obtained in fasting state, and studies suggest that peak levels have the greatest prognostic relevance [35]. This observation emphasizes the need for cautious interpretation of results and, ideally, standardization of collection time.

Fetal monitoring remains a standard in clinical practice, although its effectiveness in preventing acute events is limited. Standard methods, such as cardiotocography and Doppler ultrasound, are useful for the general assessment of fetal status, but cannot reliably predict the onset of sudden intrauterine fetal death [36]. This limitation reflects the specific pathophysiological mechanisms of ICP, in which critical events are often acute and do not precede detectable progressive changes. However, monitoring remains justified in the context of an integrated pregnancy assessment and for the identification of possible associated complications [37].

Pharmacological treatment is mainly symptomatic and adjuvant. Ursodeoxycholic acid is considered first-line therapy due to its effect on alleviating pruritus and reducing bile acid levels [38]. Its mechanism of action includes the replacement of toxic hydrophobic bile acids and the stimulation of bile secretion. However, the impact on fetal outcomes remains controversial. The PITCHES trial did not demonstrate a significant reduction in perinatal complications, suggesting that the benefits are limited mainly to the mother [39].

In cases where response to standard therapy is insufficient, adjunctive treatments, such as rifampicin, which helps to reduce bile acid levels by inducing hepatic metabolism, can be used [40]. Antihistamines may be useful for the symptomatic control of pruritus, and vitamin K supplementation is indicated in some situations to prevent bleeding complications associated with the malabsorption of fat-soluble vitamins [41]. However, these interventions do not fundamentally alter fetal risk, which

reinforces the central role of the timing of delivery.

The timing of delivery is the key management tool and the main tool for preventing intrauterine fetal death. The decision on the optimal timing is based on a balance between the risk of continuing pregnancy and that associated with prematurity. In mild forms, characterised by low bile acid levels, pregnancy can be monitored until term, in the absence of other risk factors [42]. In contrast, in moderate forms, delivery is usually planned before term, but after reaching adequate fetal maturity [43].

In severe forms, defined by elevated levels of bile acid, the risk of intrauterine fetal death becomes significant, and delivery is indicated earlier, sometimes before 36 weeks of gestation [42]. This strategy reflects a paradigm shift, in which prevention of a rare but potentially fatal event justifies early intervention, even at the cost of prematurity.

The type of delivery is not directly influenced by the presence of cholestasis but is determined by obstetric criteria. Induction of labor is commonly used and is not associated with a significant increase in caesarean section rates [44]. However, continuous fetal monitoring during labor is recommended, given the increased risk of acute fetal distress.

Despite the progress made, the management of ICP remains marked by uncertainty, especially regarding the prediction of acute events. Bile acids, although the main marker used, do not provide a perfect estimate of individual risk, and the variability of the clinical course suggests the involvement of additional factors, such as genetic susceptibility or placental function [45]. This limitation leads to a cautious approach but justified in the context of the potential severity of complications.

In conclusion, the treatment of intrahepatic cholestasis during pregnancy is cantered on reducing fetal exposure to bile acids through a combination of careful monitoring and planned delivery. In the absence of effective methods to prevent acute events, this strategy remains the most effective way to optimise the fetal prognosis.

4. Discussions

ICP remains a paradoxical clinical entity, characterized by an apparent dissociation between the severity of maternal manifestations and the potentially devastating impact on the fetus. This discrepancy has led, in recent decades, to a progressive shift in the evaluation and management paradigm, shifting the emphasis from maternal symptomatology to fetal risk stratification and prevention of acute events. In this context, the critical analysis of the available data reveals both the progress made and the persistent limitations in the understanding and management of this pathology.

One of the most important conceptual gains is the recognition of the central role of bile acids as determinants of fetal risk. Large epidemiological studies have consistently demonstrated a dose-dependent relationship between bile acid levels and the incidence of perinatal complications [32]. This observation has allowed the definition of risk thresholds and has informed current management guidelines. However, these thresholds must be interpreted with caution, as they do not reflect absolute individual risk but rather an average probability at the population level.

This limitation becomes evident in clinical practice, where there are situations in which pregnancies with relatively low levels of bile acids develop unfavourably, as well as cases in which very high levels are not associated with adverse events. This variability suggests that bile acids are necessary but insufficient as standalone predictors of fetal outcome. Consequently, a more complex approach is needed, integrating other factors such as genetic susceptibility, placental function, and duration of fetal exposure to bile acids.

Another essential aspect is related to the pathophysiological mechanisms involved in the occurrence of fetal complications.

Current data support the hypothesis that the effects of bile acids on the fetus are mediated not only by direct toxicity but also by acute functional alterations, especially at the cardiovascular level. Experimental studies have demonstrated the ability of bile acids to modify cardiac excitability, suggesting an arrhythmic mechanism for intrauterine fetal death [19,20]. This hypothesis is supported by clinical observations showing that fetal death can occur suddenly, without premonitory signs detectable by standard monitoring methods.

This feature represents one of the greatest challenges in the management of ICP and largely explains the current orientation towards proactive strategies based on labor induction before term. However, this approach raises a major problem: the risk of iatrogenic prematurity. Although preventing fetal death is a priority, preterm birth is associated with neonatal morbidity, especially in the case of moderate or late prematurity. Thus, the decision on the timing of delivery involves an inevitable trade-off between two risks, neither of which is negligible.

In this context, the current guidelines propose risk stratification based on bile acid levels, but this approach, although useful, remains imperfect. For example, the threshold of 100 µmol/L is used to define severe forms and to indicate preterm birth, but there is no evidence that this threshold represents a clear biological inflexion point. Rather, the risk increases progressively, and the use of fixed thresholds can oversimplify a complex reality.

In addition, most of the studies that underpin these recommendations are observational, which limits the ability to establish firm causal relationships. Although randomized trials are difficult to conduct in this context for ethical reasons, their lack contributes to the persistence of uncertainty. The PITCHES study, one of the few available randomized trials, highlighted the limitations of pharmacological interventions, showing that reducing bile acid levels does not necessarily translate into improved fetal outcomes [39].

This observation raises a fundamental question: to what extent are bile acids a direct causal factor versus a marker of a more complex pathological process? It is possible that they reflect only part of the hepatobiliary and placental dysfunction, and other mediators that have not yet been fully characterized, contribute to the development of complications. In this regard, recent research on the role of hormonal metabolites, inflammation, and oxidative stress offers promising perspectives but is not sufficiently integrated into clinical practice.

Another element that deserves

discussion is the role of the placenta in the pathogenesis of ICP. Although initially considered only a passive barrier, the placenta is now recognized as an active metabolic organ involved in the transport and detoxification of bile acids. Altered placental function can contribute to the accumulation of bile acids in the fetal compartment and the development of complications. However, the assessment of placental function in ICP is limited and current methods do not allow for a precise characterization of this aspect.

Regarding fetal monitoring, the available data highlight significant limitations of conventional methods. Cardiotocography and Doppler ultrasound, although useful in other pathologies, are not effective in predicting acute events in ICP [36]. This limitation reflects the distinct pathogenic mechanisms of the disease and highlights the need to develop new monitoring methods capable of detecting fetal cardiovascular or metabolic instability.

From a clinical perspective, this uncertainty translates into a precautionary approach, in which delivery is often anticipated to prevent an unpredictable event. Although this strategy is justified in the context of the risk of fetal death, it can lead to excessive interventions, especially in moderate-risk cases. Thus, there is a clear need to refine the selection criteria for labor induction to avoid both undertreatment and overtreatment. Another important issue is the variability across international guidelines, which reflects the lack of clear consensus on some issues. Although there is general convergence on the importance of bile acids and the timing of delivery, differences in recommendations suggest that the available evidence is still insufficient to support a uniform approach. This variability can create confusion in clinical practice and highlights the need for more studies.

In terms of future research directions, there are several areas of interest that could contribute to improving the management of ICP. Identifying additional biomarkers capable of reflecting the real impact on the fetus is a priority. In addition, analysis of individual bile acid fractions, and not just the total value, could provide additional information on risk. Integration of genetic data is another promising direction. The variability of the clinical response suggests the existence of individual differences in susceptibility to the effects of bile acids, and the identification of these factors could allow for a more precise risk stratification. In addition, the development of integrated predictive models, including clinical, biochemical, and genetic variables, could significantly improve the decision-making process.

Finally, a critical revaluation of existing therapeutic strategies is needed. Although ursodeoxycholic acid is widely used, its efficacy in reducing fetal risk remains uncertain. The development of new therapies, targeting specific pathogenic mechanisms, could represent an important step in improving prognosis.

In conclusion, ICPis a complex pathology, in which the interaction between biological mechanisms and clinical decisions determines the development of the fetus. Although recent advances have allowed better understanding of the disease and improved management, many aspects remain insufficiently elucidated. The current approach, based on risk stratification and early intervention, is effective in reducing the incidence of

severe events, but involves important trade-offs. The future of ICP management will depend on the ability to integrate new biomarkers and predictive models, allowing a more precise and personalized approach to this pathology.

5. Conclusions

ICP is a complex clinical entity in which the fetal impact clearly exceeds the severity of maternal manifestations, transforming this pathology into a major challenge for maternal-fetal medicine. Current data consistently support the central role of bile acids in determining perinatal risk, but this relationship, although significant at the population level, remains insufficient to allow for a precise individual prediction. Consequently, assessing the prognosis of the fetal fetus requires an integrated approach, which goes beyond the simple quantification of bile acids and includes the clinical context, the dynamics of biological parameters and individual variability.

A defining feature of ICP is the unpredictable nature of fetal complications, especially intrauterine death, which can occur suddenly, in the absence of premonitory signs detectable by conventional monitoring methods. This particularity limits the effectiveness of classic antenatal surveillance strategies and justifies the current orientation towards a preventive approach, based on reducing fetal exposure through planned delivery. Thus, the timing of delivery becomes the central element of management, reflecting a delicate balance between the risk of prematurity and that of intrauterine fetal death.

Despite the progress made in understanding the pathophysiological mechanisms and defining management strategies, many uncertainties persist. Bile acids, although the main biomarker used in clinical practice, do not provide a complete picture of fetal risk, and the variability of the clinical response suggests the involvement of additional factors, still not adequately characterized. This limitation highlights the need to develop more complex predictive models that integrate biochemical, genetic, and placental factors. From a therapeutic perspective, the use of ursodeoxycholic acid remains the current standard for improving maternal symptoms, but its impact on the fetal prognosis is limited, which highlights the lack of effective pharmacological interventions to prevent perinatal complications. In this context, delivery remains the only intervention with a direct effect on reducing fetal risk, strengthening the essential role of obstetric decision-making in the treatment of this pathology.

In the future, the improved management of ICP will depend on the ability to identify more sensitive and specific biomarkers to assess fetal risk, as well as the development of therapeutic strategies targeting specific pathogenic mechanisms. Integration of data from molecular, genetic, and clinical research could allow, in the future, a more precise and personalized approach, reducing the need for empirical interventions and optimizing perinatal outcomes.

ICP remains a pathology in which clinical decision-making is guided by risk prevention rather than certainty. The current approach, based on careful monitoring and early intervention, is effective in reducing the incidence of serious complications, but involves

important trade-offs. Progress in this field will depend on the refinement of risk assessment tools and the development of therapeutic interventions capable of truly modifying fetal development.

6. Limitations and future directions

Despite significant advances in understanding ICP, the available data presents a number of methodological and conceptual limitations that influence both the interpretation of the results and their clinical applicability. Critical analysis of these limitations is essential to contextualize the conclusions and identify future research directions.

One of the main limitations of the current literature is the prevalence of observational studies, especially retrospective cohort studies. Although these studies have contributed significantly to the definition of the relationship between bile acid levels and fetal risk, they are susceptible to selection bias, confounding, and reporting bias. In addition, variability in study design, inclusion criteria and definitions used for the diagnosis and severity of ICP limits the comparability of the results and their generalizability. Another important aspect is the heterogeneity of the populations studied. Geographic, ethnic, and socioeconomic differences can influence disease incidence, clinical expression, and response to treatment, but these variables are rarely adequately controlled in available studies. This variability contributes to the difficulty of establishing universal predictive models and emphasizes the need for multicentre studies with diverse and well-characterized populations.

The limitations of current biomarkers represent another major problem. Serum bile acids, although considered the gold standard for assessing disease severity, do not provide an accurate individual prediction of fetal risk. The relationship between their level and perinatal complications is probabilistic rather than deterministic, leading to significant uncertainty in clinical decision-making. In addition, variations related to the timing of collection, nutritional status, and laboratory methods can influence the results and complicate their interpretation. In addition, most studies focus on the total value of bile acids without considering their composition. There is evidence to suggest that certain fractions of bile acids may have different toxic potentials, but these aspects are not adequately explored and are not integrated into current clinical practice. This limitation reduces the ability to fully understand the pathogenic mechanisms and develop targeted therapeutic strategies.

Regarding fetal monitoring, the lack of methods capable of predicting acute events represents one of the most important limitations of current management. Conventional tools, such as cardiotocography and Doppler ultrasound, are useful for the overall assessment of fetal status but cannot reliably predict the sudden onset of severe complications. This gap reflects a mismatch between the pathophysiological mechanisms of the disease and the available monitoring methods. From a therapeutic perspective, the efficacy of pharmacological interventions in reducing fetal risk remains limited. Although ursodeoxycholic acid is widely used and is effective in improving maternal symptoms, its impact on perinatal outcomes is not clearly

demonstrated. The lack of therapies capable of directly modifying pathogenic mechanisms highlights the need to develop novel therapeutic approaches directed at specific molecular targets.

Another element worth mentioning is the lack of integrated predictive models. Currently, clinical decisions are mainly based on bile acid levels and gestational age, without including other relevant factors such as genetic characteristics, placental function, or emerging biomarkers. This simplified approach may lead to suboptimal decisions, either through premature interventions or underestimating risk.

In this context, future research directions should primarily focus on identifying more sensitive and specific biomarkers to assess fetal risk. Studies on hormonal metabolites, oxidative stress markers, and complete bile acid profiles could provide additional relevant information. In addition, the development of advanced analysis techniques, such as metabolomics and proteomics, could contribute to the identification of biological signatures associated with increased risk.

Integration of genetic data is another promising direction. The identification of genetic variants associated with susceptibility to ICP and fetal response to bile acid exposure could allow for more precise risk stratification and personalized treatment. In this regard, studies exploring the role of genes involved in bile acid transport and hormonal metabolism are particularly relevant. There is also a need to develop integrated predictive models that combine clinical, biochemical and genetic variables in a unified framework. The use of artificial intelligence and machine learning algorithms could facilitate the analysis of complex data sets and contribute to improving the accuracy of the prediction.

Regarding fetal monitoring, future research should focus on developing methods capable of detecting acute functional changes, especially at the cardiovascular level. Advanced imaging and monitoring techniques, such as detailed fetal echocardiography or heart rate variability analysis, could provide new insights in this area. Finally, a critical revaluation of current therapeutic strategies is needed. The development of new therapies, targeting the molecular mechanisms involved in ICP, could represent an important step in reducing fetal risk. In this regard, research on modulators of nuclear receptors, bile acid transporters, and other molecular targets is particularly promising.

Although significant progress has been made in understanding and managing ICP, numerous limitations remain. Overcoming these will require a multidisciplinary and integrated approach that combines basic and clinical research and allows the development of more precise and effective strategies to optimize the fetal prognosis.

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