Review Article

The Genetic and Epigenetic Nexus of Intrahepatic Cholestasis of Pregnancy in the In Vitro Fertilization Era: A Perspective on the Iranian Population

Akram Hamzavi [1,2] , Tayebeh Hamzehloei [1,3*]

[1] Genetics Department, Medical School, Mashhad University of Medical Sciences, Mashhad, Iran

[2] Medical Genetics Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

[3] Metabolic Syndrome Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

ABSTRACT

Intrahepatic cholestasis of pregnancy (ICP) is a gestational liver disorder associated with significant fetal risks. Its incidence is notably increased in pregnancies conceived via in vitro fertilization (IVF). This elevated risk is attributed to the supraphysiological hormonal environment created during controlled ovarian hyperstimulation, which may act as a trigger in genetically susceptible individuals. The etiology of ICP involves a complex interplay between a predisposing genetic background, primarily mutations in hepatobiliary transporter genes like ABCB4 and ABCB11, and regulatory epigenetic mechanisms. Epigenetic modifications, such as DNA methylation and microRNA-mediated silencing, are increasingly recognized as key mediators that could translate the hormonal stimulus of IVF into the clinical phenotype of cholestasis. While the genetic architecture of ICP has been explored in several ethnic groups, a significant knowledge gap exists for the Iranian population—a population with a unique genetic heritage and a growing reliance on assisted reproductive technologies (ART). This review examines the genetic and epigenetic underpinnings of ICP, focusing on how the hormonal milieu of IVF unmasks latent predispositions. We highlight the urgent need for research within the Iranian population to develop tailored genetic screening protocols for ART candidates, aiming to mitigate the risk and improve perinatal outcomes in this high-risk group.

Keywords: Intrahepatic Cholestasis of Pregnancy (ICP), In Vitro Fertilization (IVF), Genetics, Epigenetics, Iranian population, ABCB4, ABCB11, Hormonal stimulation

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**Corresponding Author:*
Tayebeh Hamzehloei, PhD Medical Genetics, Associate professor of Medical Genetics Department of Mashhad University of medical science.

Address : Genetics Department, Medical School, Mashhad University of Medical Sciences, Mashhad, Mashhad-Iran
Tel: + 98 5138002248
Fax: + 98 5138002246
Email: hamzehloiet@mums.ac.ir

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is the most common reversible liver disorder of gestation, characterized by maternal pruritus and elevated serum bile acids (1). While the maternal prognosis is excellent, ICP is fraught with perinatal risks, including spontaneous preterm birth, fetal distress, and intrauterine fetal demise, particularly when maternal bile acid levels are severely elevated (2). The pathogenesis of ICP is understood to be multifactorial, arising from a complex interplay of genetic, hormonal, and environmental factors (3).

This perspective synthesizes existing literature to propose a hypothesis-driven framework for understanding IVF-associated ICP in the Iranian population. The widespread adoption of Assisted reproductive technologies (ART) has introduced a new dimension to ICP risk. Multiple meta-analyses have now confirmed that pregnancies conceived via IVF have a significantly higher incidence of ICP compared with spontaneously conceived pregnancies, with some studies reporting a nearly doubled risk (4, 5). This strong association is attributed to the controlled ovarian hyperstimulation (COH) protocols central to IVF, which result in supraphysiological concentrations of estrogen and progesterone (6). These hormones are known to have cholestatic properties, which can impair bile acid transport in genetically susceptible individuals (7, 8).

This creates a "two-hit" model for ICP in the context of IVF (Figure 1). The first "hit" is a pre-existing genetic susceptibility, often a heterozygous, clinically silent mutation. The second "hit" is the intense hormonal stimulus from IVF, which overwhelms the already compromised biliary transport system, leading to the clinical manifestation of ICP (9). This review synthesizes our current understanding of these factors, with a specific focus on the implications for the understudied Iranian population.

The Genetic Architecture of ICP: A Pre-existing Vulnerability

The strong genetic basis of ICP is well-established, with a significant proportion of cases linked to heterozygous mutations in genes encoding hepatobiliary canalicular transport proteins (8). These mutations create a subclinical defect that only becomes apparent under cholestatic stress.

Principal Transporter Gene Defects

Mutations in ATP-binding cassette (ABC) transporter genes are the most common genetic determinants of ICP.

• **ABCB4 (MDR3):** This gene's product translocates phospholipids into the bile, protecting the biliary tree from the detergent action of bile salts. Heterozygous ABCB4 mutations were one of the first genetic links to ICP to be described and are a major cause of the disease (10).

• **ABCB11 (BSEP):** This gene encodes the primary bile salt export pump. Defects in ABCB11 directly impair bile salt secretion from hepatocytes, leading to intracellular accumulation. Variants in this gene are often associated with more severe ICP phenotypes (11) and the heightened risk of fetal complications linked to high bile acid levels (2).

• **Other Genes:** Variants in other genes such as ATP8B1, the tight junction protein TJP2 (12), and the nuclear bile acid receptor NR1H4 (FXR) (13) have also been identified as risk factors, expanding the list of candidate genes for this complex disorder (Table 1).

IVF does not cause these mutations, but it provides the potent trigger that reveals their functional consequence.

Table 1. Key Genes Implicated in Intrahepatic Cholestasis of Pregnancy

Gene	Protein	| Function in hepatocyte	Role in IVF-associated ICP	Reference
ABCB4	MDR3	Phospholipid transport	Impaired function unmasked by high hormone levels	Jacquemin et al., 1999
ABCB11	BSEP	Bile salt export	Reduced capacity overwhelmed by hormonal inhibition	Pauli-Magnus et al., 2004
ATP8B1	FIC1	Membrane stability	Reduced membrane integrity under cholestatic stress	Piechota & Jelski, 2020
TJP2	TJP2	Tight junction integrity	Increased "leakiness" exacerbated by hormone effects	Sambrotta et al., 2014
NR1H4	FXR	Bile acid sensor/ regulator	Dysregulation impairs feedback control of bile acids	Claudel et al., 2005

The IVF Connection: A Powerful Epigenetic Modulator

The supraphysiological hormone levels in IVF are not just a simple trigger. We hypothesize that they may likely exert their effects through epigenetic modifications that regulate the expression of key transporter genes. Epigenetics provides the molecular link between the hormonal

environment of IVF and the genetic susceptibility of the patient (14).

DNA Methylation

Estrogen metabolites have been shown to influence DNA methylation, an epigenetic mechanism that can silence gene expression. A recent case-control study revealed altered methylation patterns in the promoter regions of genes involved in bile acid transport in the blood of women with ICP (15). However, this study did not specifically examine IVF-conceived pregnancies. Therefore, it does not directly demonstrate that hormonal stimulation in IVF induces these epigenetic changes. Nevertheless, it is plausible that high estrogen levels during COH could induce hypermethylation at the promoters of genes such as ABCB4 and ABCB11, thereby dramatically reducing their transcription and precipitating cholestasis.

MicroRNA (miRNA) Regulation

miRNAs are small non-coding RNAs that can inhibit gene expression post-transcriptionally. In cholestatic conditions, specific miRNAs that target the mRNA of bile transporters have been identified. For example, miR-29a has been shown to epigenetically regulate FXR (NR1H4), a master regulator of bile acid homeostasis (16). Importantly, this study was conducted in the context of hepatic steatosis, not ICP or IVF. Despite this limitation, we hypothesize that in IVF, hormonal shifts might alter the miRNA landscape, providing another rapid mechanism for reducing the amount of functional transporter protein and contributing to ICP.

The Unexplored Frontier: The Iranian IVF Population

Despite the clear association between IVF and ICP, research on the specific genetic risk factors across diverse populations remains severely lacking. Comprehensive reviews of ICP genetics highlight the concentration of research in European, Asian, and South American populations, with a notable absence of data from the Middle East (3). This knowledge gap is particularly concerning for the Iranian population for several reasons:

1. **Unique Genetic Background:** The Iranian gene pool is distinct from that of well-studied cohorts. It is highly likely that population-specific or novel founder mutations in ICP-associated genes exist.
2. **History of Consanguinity:** A historical tradition of consanguineous marriages, though declining, may have enriched the frequency of certain recessive alleles, potentially increasing the prevalence of heterozygous carrier states relevant to ICP.
3. **Increasing Use of ART:** Iran has a well-established and growing network of ART clinics, meaning an increasing number of women are being exposed to the hormonal triggers that can induce ICP.

Without population-specific data, clinicians cannot effectively screen or counsel patients, and genetic tests developed for other ethnicities may fail to identify at-risk Iranian women undergoing IVF.

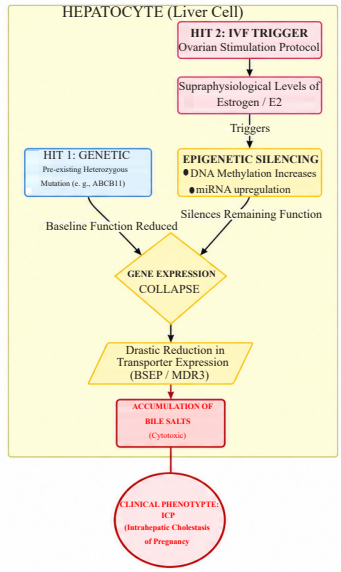

Figure 1.The "Two-Hit" hypothesis for IVF-associated ICP. The first "hit" is a pre-existing genetic susceptibility (e.g., heterozygous mutations in ABCB4, ABCB11, or other transporter genes). The second "hit" is the supraphysiological hormonal environment created by controlled ovarian hyperstimulation (COH) during IVF. In a genetically susceptible individual, this hormonal stimulus may overwhelm the compromised biliary transport system, leading to the clinical manifestation of ICP. Women without genetic susceptibility typically have sufficient reserve capacity to maintain normal bile acid homeostasis despite hormonal stimulation.

Limitations

As a perspective piece synthesizing existing literature, several limitations must be acknowledged:

Lack of Direct Evidence: There is currently no direct evidence linking IVF hormonal stimulation to specific epigenetic changes (DNA methylation or miRNA profiles) in the context of ICP. The cited studies on DNA methylation (15) and miRNA regulation (16) were conducted in general ICP populations or other liver conditions, not specifically in IVF-conceived pregnancies. Therefore, the proposed epigenetic mechanisms remain hypothetical.

Absence of Iranian Genetic Data: No published studies have characterized the prevalence or spectrum of ABCB4, ABCB11, or other ICP-associated gene variants specifically in the Iranian population. This limits our ability to estimate baseline risk or design targeted screening panels.

Low Penetrance of Heterozygous Mutations: Heterozygous mutations in transporter genes have low penetrance, meaning that most carriers do not develop ICP even under hormonal stimulation. This presents a significant challenge for pre-IVF genetic screening, as the positive predictive value of identifying a variant would be low, potentially leading to unnecessary anxiety or altered management for many women who would never develop the condition.

Confounding Factors: The association between IVF and ICP may be influenced by other factors not discussed in this perspective, including maternal age, parity, multiple gestation (more common in IVF), and underlying infertility etiologies.

Conclusion and Future Clinical Perspectives

IVF-associated ICP is a prime example of a gene-environment interaction, where the "environment" is a powerful iatrogenic hormonal stimulus. The condition is not caused by IVF, but possibly by an underlying genetic susceptibility that is potentially unmasked by the procedure. We hypothesize that epigenetic mechanisms may be are the likely transducers of this hormonal signal.

The absence of data from the Iranian population is a major gap in our global understanding and a barrier to providing optimal care. A focused research strategy is imperative and should include:

• Prospective Cohort Studies: Following Iranian women undergoing IVF to determine the precise incidence of ICP and collect biological samples.

• Genetic Screening: Performing next-generation sequencing on Iranian ICP patients to identify the population-specific mutation spectrum.

• Pre-IVF Risk Stratification: The ultimate goal is to develop a genetic screening panel that can identify high-risk women before they undergo COH, allowing for modified stimulation protocols or heightened surveillance.

• Epigenomic Analysis: Investigating changes in DNA methylation and miRNA profiles in response to ovarian stimulation in Iranian IVF patients to identify biomarkers of risk.

By elucidating the unique genetic and epigenetic landscape of ICP in the Iranian population, we can move towards a future of personalized reproductive medicine, making IVF safer and improving perinatal outcomes.

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