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Review Article

Intrahepatic Cholestasis and Fetal Demise: Association or Causation?

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1. Abstract

1.1. Objective: To review the available information about the potential association of intrahepatic cholestasis of pregnancy (ICP) and stillbirth.

1.2. Method: Scholarly review of relevant studies.

1.3. Results: Data are conflicting regarding a cause and effect relationship between ICP and stillbirth. On one hand, the data show a higher risk of stillbirth at term without an effective test that might predict demise except high level of bile acids. On the other, even if the stillbirth rate is reduced by a late preterm birth, one must appreciate the cost of active management in terms of morbidity due to induction, failed induction, unnecessary cesareans, and outcomes related to late preterm births. A cause and effect relationship between ICP and stillbirth is unlikely according to Hill's criteria for causation.

1.4. Conclusions: Better understanding of the underlying mechanism of ICP causing fetal demise is still required to define a cause and effect relationship.

2. Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a relatively common disease during pregnancy [1,2]. The specific clinical findings of ICP are pruritus (especially in the palms and soles), high levels of total serum bile acids and/or liver transaminases in the late second and third trimester of pregnancy, and their spontaneous resolution after delivery [2]. The incidence of ICP in Europe is estimated as 0.5 to 1.5% [3]. The etiology of the disease is multifactorial and largely unknown. Chronic hepatitis C, multiple gestation, prior history or family history of ICP, and advanced maternal age were found to be associated with ICP[4].

ICP is associated with several adverse outcomes, such as stillbirth, spontaneous and iatrogenic preterm birth, meconium stained amniotic fluid, and neonatal distress [5, 6]. However, pregnancy outcome is normal in the majority of cases.

The mechanism leading to fetal demise in ICP is not yet entirely understood and thus may cause confusion regarding the appropriate management of such cases [2,7] Maternal bile acids cross the placental barrier and might accumulate in the fetal compartment, with impeded clearance of bile acids because of the reversed transplacental gradients in ICP [8]. Because bile acids appear to be toxic to cardiomyocytes and induce vasoconstriction in the placental chorionic and umbilical veins, some evidence exists to suggest that