Still Birth Risk and Intrahepatic Cholestasis of Pregnancy is Still a Dilemma; Is Active Management Required?

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Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disorder characterized by mild to severe pruritus and disturbed liver function tests. Although ICP has favorable outcome for mothers; prematurity, meconium-stained amniotic fluid, intrauterine demise and an increased risk for neonatal respiratory distress syndrome are thought to be major concerns for fetus [1]. This relatively benign maternal condition had been reported to be associated with an increased rate of unexplained term still birth that occurs between 37 and 39 weeks of gestation. Exact mechanism of fetal death that is associated with ICP is unknown, there is evidence to suggest that it may be related to a fetal cardiac event including bile acid-induced cardiac arrhythmias, impaired contractility and chorionic vein constriction [2]. Williamson et al. assessed the effect of taurocholate on cardiomyocyte in a series of in vitro murine study. Taurocholate resulted in loss of cardiomyocyte contractile function [3]. Also Kotake et al. reported that high levels of taurocholate depress action potentials of the sinoatrial node and notably induce bradycardia in rabbits [4]. Besides fetal cardiac events, bile acids have found to induce vasoconstriction in human placental chorionic veins and umbilical vein constriction. Oxidative stress in the placenta causing acute anoxia rather than chronic anoxia due to these vascular events are thought to be associated with still birth [5].

Prediction of still birth

Several studies have attempted to find the predictors of fetal death in women with ICP. Increased total bile acid level (TBA) level has been associated with increased risk of still birth as well as meconium staining, low apgar scores, preterm birth. Glantz et al reported an increase risk of still birth in women with TBA levels >40 mmol/l [6]. Geenes et al’s study including women with ICP and TBA >40 mmol/l, the incidence of still birth was 1.5 percent, which was higher than the control population incidence of 0.5 percent. Ten still births were reported in this study and 6 of them occurred before 37 gestational weeks with a median TBA of 137 mmol/l [7]. Kawakita et al reported outcomes of 233 women with ICP. There were 4 still births occurred at 24-37 weeks of gestation and all of them had TBA level >100 mmol/L. Three of these 4 cases were reported to be followed by weekly or twice weekly biophysical profiles and had reassuring findings within 1 week of still birth; demonstrating the unpredictable nature of the disease [8]. However, still births have been reported with TBA concentrations below 40 mmol/l. But still births with lower bile acid levels are only based on case reports. Sentilhes et al reported a case of still birth at 39 weeks of gestation with ICP who had responded well to ursodeoxycholic acid, demonstrated by a low bile acid value (13 mmol/l) at 28 weeks [9]. Similarly Lee et al. reported a case of ICP at 28 weeks with TBA level of 13 mmol/ml who had fetal death at 34 weeks of gestation [10].

Still Birth Risk for Intrahepatic Cholestasis of Pregnancy

Limited evidence regarding the usefulness of TBA and also antenatal fetal testing in the prediction and prevention of still birth, reduction in the risk of still birth with ursodeoxycholic acid and increased still birth rates after 37 weeks compared with normal normal pregnancies make the management more complicated.

To avoid these theoretical late term still births, there has been international acceptance of active management of ICP-affected pregnancies with the goal of delivering the infant at <39 weeks' gestation. The general agreement suggests that delivery should not be delayed after 37-38 wk of gestation in patients with ICP but not all obstetric professionals accept the association between ICP and still birth or agree with the concept of active management in ICP. Although American College of Obstetricians and Gynecologists Committee and the Society for Maternal Fetal Medicine endorsed active management of ICP-affected pregnancies [11], RCOG reported that active management of ICP should be replaced by individual management decisions according to the evidence concerning the known perinatal risk of early term birth vs the small but unknown risk of ICP-associated term still birth [12].

Previous reports of adverse perinatal outcome primarily focused on increased perinatal mortality rates due to result of prematurity sequale. Recent reports narrowed perinatal concern to avoiding unexplained term still births. Unfortunately, randomized clinical trials to support active management with labor induction to prevent intraterine fetal demise and consensus for obstetric management in ICP are lacking. Recently Henderson et al. evaluated 16 articles .published between 1986 and 2011, supporting ICP as a medical indication for early term delivery and the evolution of active management protocols for ICP. In the 6 uncontrolled study between 1967 and 1983, 4 unexplained term still births in 331 ICP-affected pregnancies were documented. These articles became the core reports that linked ICP to unexplained term still births before active management of ICP-affected pregnancies with the goal of delivery <39 weeks gestation became common practice. Although these articles are cited as evidence of ICP-associated still birth risk, the 1.2% still birth rate (4/331) in this group was similar to the background still birth rates of 1.1% (11/1000) and 0.6% (6/1000) in 1967 and 2011, respectively. After active management has been empirically adapted into clinical practice after 1980 and 10 reports became the evidence based support for active management. Likewise still birth rates were similar to their respective national still birth rates. Authors reported no evidence to support the practice of active management for ICP and recommended individual management of ICP-affected pregnancies rather than routine implementation of an active management protocol [13].

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Recently, Puljic et al. evaluated the risk of infant and fetal death by each additional week of expectant management vs immediate delivery in 1.604.386 singleton pregnancy with and without ICP. For each week of gestation; the risk of still birth defined as fetal demise at or after 20 weeks' gestation, the risk delivery represented by the risk of infant death following delivery at a given week of gestation and the composite mortality risk of expectant management for 1 additional week were assessed for both ICP and control group. The risk of still birth was higher in women with ICP than in control group at each gestational age between 34 and 40 weeks (overall 63.8 vs. 21.2 per 10000; p<0.001). The risk of infant death was reported to be lowest at 36 weeks and increased thereafter in women with ICP. In contrast the risk of delivery reached a nadir at 39 weeks (9.8 per 10000) in women without ICP. In women with ICP, the risk of delivery was lower than the risk of expectant management at 36 weeks' gestation (4.7 per 10,000 vs. 19.2 per 10,000). After 36 weeks' gestation, the risk of expectant management remained higher than delivery and continued to rise at each week of gestation thereafter. Authors recommended delivery at 36 weeks' gestation to reduce fetal, neonatal and infant mortality [14].

But previous reports and guidelines continue to grow the discussion whether active management does reduce the still birth risk or not and when to perform delivery? The major problem is that the small number of cases with still birth in ICP cases. Even large cohort studies, like Puljic et al.'s study, do not provide sufficient number of cases. Page et al. reported the number of cases as 35737 (each ICP and control group) for a randomized controlled trial that will able to demonstrate a real reduction of still birth in the ICP group [15].

Conclusion

In the light of current evidence, active management can not be recommended or refused in cases with ICP.

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