Management of intrahepatic cholestasis in pregnancy

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Intrahepatic cholestasis of pregnancy is a complication in 0·2–2% of pregnancies,[1] causing pruritis and increased serum bile acids, liver transaminases, and, occasionally, bilirubin. It has been associated with severe adverse pregnancy outcomes, including fetal distress, spontaneous and iatrogenic preterm birth, and stillbirth,[1] for which no effective treatment is yet known.[2] Ursodeoxycholic acid, which is regularly prescribed, improves biochemical parameters and reduces, although on a limited scale (evidence is conflicting), pruritis.[3] Antenatal fetal monitoring strategies have not proven effective, resulting in substantial variation in the timing of delivery due to attempts to balance risks of stillbirth against increasingly understood neonatal and childhood complications from late preterm and early term delivery.[4,5] This problem is reflected in the scarcity of national guidelines worldwide. The guidelines published in 2011 by the Royal College of Obstetricians and Gynaecologists encourage open discussion with women about the scarce evidence supporting early term delivery to minimise stillbirth risk.[6] However, subsequent authors have used decision analytic techniques to recommend delivery at 36 weeks of gestation.[7]

In the context of this uncertainty, in *The Lancet*, Caroline Ovadia and colleagues[8] aim to clarify the association of biochemical markers and adverse perinatal outcomes. They did an aggregate meta-analysis of 23 studies comparing perinatal outcomes of women with intrahepatic cholestasis of pregnancy (n=5557) with healthy controls (n=165 136), as well as the first individual patient data (IPD) meta-analysis from 27 studies exploring the association between perinatal outcomes and biochemical markers in 5269 pregnancies. Their aggregate meta-analysis shows evidence of the associations of intrahepatic cholestasis of pregnancy with increased risks of stillbirth (odds ratio 1·46 [95% CI 0·73–2·89]), spontaneous preterm birth (3·47 [3·06–3·95]), iatrogenic preterm birth (3·65 [1·94–6·85]), meconium stained liquor (2·60 [1·62–4·16]), and neonatal unit admission (2·12 [1·48–3·03]) compared with healthy controls.

Importantly, the IPD meta-analysis shows that elevated total bile acid concentrations are highly predictive for stillbirth in singleton pregnancies (area under the receiver operating characteristic curve 0·83 [95% CI 0·74–0·92]). This finding provides some guidance to clinicians, since it shows the increased stillbirth numbers only exceeded those of the general population once total bile acid concentrations were of 100 µmol/L or more; the stillbirth prevalence after 24 weeks of gestation was 3·44% (95% CI 2·05–5·37) for women with intrahepatic cholestasis of pregnancy compared with 0·3–0·4% from pooled national average data among included countries. Usefully, the authors associated a cutoff concentration with clinically relevant outcomes, rather than basing it on the 95th percentile of the normal distribution. Clinicians and women can be reassured that stillbirth rates seem similar to the general population while total bile acid concentrations remain less than 100 µmol/L; however, weekly testing is advised because the increase in total bile acids with advancing gestation[9] might increase the stillbirth risk. The issues clinicians faced in balancing the risks of stillbirth against those of late preterm or early term delivery might thus be resolved without the use of an intervention study. In comparison, in women with total bile acid concentrations of 100 µmol/L or more, delivery should probably occur by 35–36 weeks of gestation. Since this is the minority of women with intrahepatic cholestasis of pregnancy, overall, a reduction in iatrogenic preterm birth due to intrahepatic cholestasis of pregnancy is to be expected.

IPD studies have limitations. Bias remains a possibility depending on the quality of data collected by the initial

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trialists, specifically in unblinded studies, in which high bile acid concentrations might have been a reason for induction. Also, excluding stillbirth, adverse pregnancy outcomes have been defined differently between individually included studies. The development of core outcome sets should assist with ongoing improvement in data for IPD analysis in the future.

However, IPD provide some evidence on predictors of clinically meaningful outcomes, such as stillbirth, for which it is difficult for individual studies to reach adequate power. Furthermore, the use of existing data improves efficiency, timely provision of information, and cost-effectiveness in research, none of which could be achieved by a new, adequately powered cohort study.

Development of international networks facilitates optimal data use in future studies. Such collaborations could assist in addressing the concerns of bias relating to stillbirth risk beyond 37 weeks among those women with bile acids of less than 100 µmol/L because of the high numbers of iatrogenic deliveries. For example, the IPD analysis included trials from China done during a period when delivery for intrahepatic cholestasis of pregnancy with bile acid of 40 µmol/L or more at 37 completed weeks was recommended. Liu and colleagues[10] did a large cohort study of 1319 cases of intrahepatic cholestasis of pregnancy that was not included in this IPD analysis. On excluding 11 cases of intrahepatic cholestasis of pregnancy with bile acids of 100 µmol/L or more, the 163 cases with bile acids of 40–99 µmol/L were not associated with increased stillbirth risk.[10] This supports Ovadia and colleagues' findings and indicates that a threshold of 100 µmol/L or more is also applicable in a Chinese population, where the incidence of intrahepatic cholestasis of pregnancy is high.[8]

Although important questions such as the benefit of ursodeoxycholic acid for reducing stillbirth remain, the approach of Ovadia and colleagues[8] paves the way for improving the clinical management of conditions with rare, but devastating, outcomes.

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Immune response to non-HLA antigens and renal allograft loss

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Pioneering work first identified IgG antibodies binding specifically to donor HLA class I and class II molecules (donor-specific antibodies) as a major barrier to successful transplantation.[1] Antibody-directed immune responses to kidney allografts are notable for the severity of injury and the propensity for graft failure. In the USA, de-novo donor-specific antibody development is responsible for most allograft losses due to chronic antibody-mediated rejection.[2] Although the clinical relevance and pathogenic potential of HLA donor-specific antibodies is well established, other non-HLA antibodies with pathogenic potential have been described, including antibodies to AT1R, ETAR, and LG3, as well as natural antibodies, which bind to immunogenic self-determinants, including oxidation-related cell surface antigens.[3–7] Furthermore, we have noted an increasing number of patients who