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Intrahepatic cholestasis of pregnancy is associated with an increased risk of gestational diabetes

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ABSTRACT

Objective: To evaluate the association between intrahepatic cholestasis of pregnancy (ICP) and gestational diabetes mellitus (GDM).
Study design: A retrospective case-control study of pregnancy outcomes in 57,724 women managed at a university teaching hospital in Rhode Island, USA, in whom universal screening for GDM had been performed and who were assessed for the incidence of ICP. Pregnancies complicated by ICP or GDM between February 2005 and June 2011 were identified from the electronic patient records using appropriate ICD codes. A total of 125 cases were required to detect a difference in the incidence of GDM in ICP at 5% significance with 80% power. Demographic and clinical outcome data (including maternal age, ethnic group, BMI, and infant weight and gender) were also collected.
Results: Of the 57,724 pregnancies, 143 were complicated by ICP (0.25%) and 4880 by GDM (8.5%). Nineteen ICP cases had GDM. The incidence of GDM in ICP was 13.6% (19/140, OR 1.68 CI 1.04–2.72). Where gestational ages were available ($n = 105$), of those screened for GDM prior to developing ICP, 13.4% (11/82, OR 1.64 CI 0.88–3.06) had a confirmed diagnosis, rising to 30% (7/23, OR 4.69 CI 1.98–11.1) in cases that were screened following the onset of cholestasis. Simple linear regression analysis of adjusted birth weight centiles in ICP revealed a significant linear trend of increasing centiles with gestational age ($p = 0.005$).
Conclusions: These data support the hypothesis that the incidence of GDM is higher in women predisposed to developing ICP. It is likely that this susceptibility increases further following the onset of cholestasis.

1. Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a liver disease specific to pregnancy, characterised by maternal pruritus, elevated maternal serum bile acids and liver transaminases. It is associated with adverse pregnancy outcomes, including spontaneous preterm labour, fetal hypoxia, meconium-stained liquor and stillbirth. The prevalence of ICP varies from as high as 5% in Chile to 0.7% in the UK [1]. Prospective studies in Sweden [2] and the UK [3] demonstrated that the risk of adverse pregnancy outcomes is significantly increased when maternal serum bile acid levels rise above 40 μmol/L. These findings are in agreement with six other studies [4–9]. The aetiology of ICP is multifactorial, with susceptibility conferred by environmental, endocrine and genetic factors [1]. There are accumulating data to show that normal pregnancy is mildly cholestatic [10]. It is likely that ICP occurs in women who are unable to maintain adequate bile acid homeostasis in the presence of normal gestational alterations in the relevant hepatic metabolic pathways. There are also studies demonstrating a relationship between bile acid, cholesterol and glucose homeostasis [11–13] in which the primary bile acid receptor farnesoid X receptor (FXR) is reported to influence normal glucose homeostasis as well as pathways involved in cholesterol metabolism [14]. It is therefore possible that women predisposed to metabolic dysregulation of one of these pathways may also be at increased risk of a disorder in another.

Previous studies have demonstrated impaired glucose tolerance and dyslipidaemia in women with ICP [15–18], but to the best of our knowledge none has examined the temporal relationship between gestational diabetes mellitus (GDM) and ICP. We

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hypothesised that ICP is associated with an increased incidence of GDM and that this is the result of aberrant bile acid homeostasis. The aim of this study was to investigate the association between ICP and GDM in a cohort of pregnant women with ICP who had undergone routine screening for GDM.

2. Materials and methods

Following approval from the Women and Infants Hospital (WIH) institutional review board (reference: 11-0010), cases of ICP between February 2005 and June 2011 were identified by searching the Electronic Patient Records (EPR) of the hospital, using International Classification of Disease Codes (Table 1). ICP was diagnosed in women with new onset pruritus in conjunction with abnormal liver enzymes and/or elevated bile acids (over 10 μmol/L) in the absence of any additional identifiable liver disorder (Table 2).

Pregnancies complicated by ICP were subject to the following management in accordance with the hospital's guidelines: (1) Women with severe cholestasis (>40 μmol/L, serum ALT > 300 IU/L, or severe pruritus non-responsive to therapy) are offered induction of labour at 37 weeks or amniocentesis at 36 weeks to assess fetal lung maturity, with subsequent induction if mature. (2) Women with mild cholestasis are offered induction of labour at 39 weeks or amniocentesis at 37 weeks to assess fetal lung maturity, with subsequent induction if mature. The WIH is responsible for 75% of all deliveries in the state of Rhode Island. Screening for GDM was offered to all pregnant women managed at the hospital, in accordance with the American College of Obstetricians & Gynaecologists guidelines 2001–11 [19]. Uptake of GDM screening was in excess of 90%, and comprised a random glucose challenge test (GCT) of 50 g of glucose taken in the second half of the pregnancy, followed by a blood glucose measurement after 1 h. If the blood glucose was in excess of 130 mg/dl (7.2 mmol/l) a 100 g 3-h glucose tolerance test (GTT) was performed, with a diagnosis of GDM confirmed if two blood glucose readings were above the following levels: fasting 95 mg/dl (5.3 mmol/l), 1 h 180 mg/dl (10.0 mmol/l), 2 h 155 mg/dl (8.6 mmol/l), 3 h 140 mg/dl (7.8 mmol/l).

Inclusion criteria for GDM in this study were a positive GCT and GTT. In women testing positive for GDM, however, the gestational age at which the diagnosis was made was defined as the date of the initial positive screening test. If a woman had a negative GTT, regardless of the result of the GCT, she was considered to have normal glucose tolerance and no repeat GTT testing was performed unless clinically indicated.

The control group was drawn from hospital records at WIH of all deliveries over the same period, including those complicated by GDM (Table 1). For comparison, cases of preconception diabetes (Table 1) were removed from both the ICP and control groups (Fig. 1).

Given the potential influence of aberrant bile acid metabolism on glucose homeostasis, the incidence of GDM in ICP was compared to that of all other pregnancies delivered at the hospital over the same time period.

In all cases of ICP, where available, additional demographic and clinical outcome data regarding potential confounders, including maternal age, racial group, BMI, and infant weight and gender, were also collected from the hospital's EPR system. Given the size of the control group, however, these data were collated in aggregate. As the WIH is the only tertiary perinatal service in Rhode Island, the incidence of pregnancies complicated by ICP and preterm delivery (PTD) at the hospital was compared against that of all preterm deliveries in the state, as this was considered to be a better reflection of the incidence of PTD in the general pregnant population [20].

Data analysis was performed with the software packages SAS version 9.2 and STATA 10. Proportions, means, medians, and ranges were computed as descriptive statistics. Categorical variables were compared by Chi-square or Fisher's exact test and continuous variables were compared by *T*-test. The exact binomial method was employed to estimate 95% confidence intervals (CI) for proportions. Odds ratios (ORs) were computed as measures of association between ICP and patient racial group, GDM, and pregnancy outcomes. Multiple logistic regression was used to adjust for racial group as a potential confounder of the association between ICP and GDM. In ICP birth weight centiles for singleton pregnancies were adjusted for maternal BMI, parity and race as well as infant gender using software GROW^{TM} v6.1 (USA). Simple linear regression was used to test for a linear trend in mean birth weight centile across 35–39 weeks of gestation. Control data were available in aggregate, and thus it was not possible to statistically adjust for maternal age and BMI. In the event that some data regarding pregnancy outcome were not available they were omitted, with the denominator indicating the number of results available for analysis.

Two-tailed *p*-values were presented with $p < 0.05$ considered statistically significant.

Table 1
Study international classification of diseases codes.

Disease	ICD code	Condition
ICP	646.7, 646.71, 646.73	Liver and biliary tract disorders in pregnancy.
ICP	576.8, 751.69	Other specified disorders of biliary tract.
ICP	794.8	Non-specific abnormal results of function study of liver.
GDM	648.81, 648.83	Abnormal glucose tolerance of mother, delivered, with or without mention of antepartum condition.
DM	648.01, 648.03	Diabetes mellitus of mother, complicating pregnancy, childbirth, or the puerperium.

ICD codes used to identify pregnancies complicated by Intrahepatic Cholestasis of Pregnancy (ICP), Gestational Diabetes Mellitus (GDM) and preconception Diabetes Mellitus (DM). NB: if a patient had more than one ICD codes for the same condition they were only counted once with which ever code was entered first.

Table 2
Biochemical parameters of Intrahepatic Cholestasis of Pregnancy (ICP) at diagnosis.

Blood result at diagnosis of ICP	Mean	Median and range
Serum bile acid	40 μmol/L	21 (4–249)
Alanine transaminase	129 U/L	83 (11–886)
Total bilirubin	14 μmol/L	12 (5–75)

Blood results from women with a new diagnosis of ICP managed at Women and Infants Hospital RI from February 2005 to June 2011.

3. Results

Of the 57,724 pregnancies recorded between February 2005 and June 2011, 143 were complicated by ICP (0.25%), 4880 by GDM (8.5%) and 593 by preconception diabetes (1.0%). An average maternal age of 28.5 years (±6) was recorded for all non-cholestatic pregnancies over the study period, compared to 28.4 years (±6) in those complicated by ICP ($p = 0.8$). The median gestational age at diagnosis of ICP was 33 weeks (range 12–39), and 9% of these women tested positive for hepatitis C.

Hispanic women more commonly had pregnancies complicated by ICP (Table 3). Compared to the control group the incidence of GDM in pregnancies complicated by ICP was 13.6% (OR 1.68 CI 1.04–2.72, $p = 0.03$). When the ICP group was divided into women