The Metabolic Profile of Intrahepatic Cholestasis of Pregnancy Is Associated With Impaired Glucose Tolerance, Dyslipidemia, and Increased Fetal Growth

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Diabetes Care 2015;38:243–248 | DOI: 10.2337/dc14-2143

OBJECTIVE

Quantification of changes in glucose and lipid concentrations in women with intrahepatic cholestasis of pregnancy (ICP) and uncomplicated pregnancy and study of their influence on fetal growth.

RESEARCH DESIGN AND METHODS

A prospective study comparing metabolic outcomes in cholestastic and uncomplicated singleton pregnancies was undertaken at two university hospitals in the U.K. and U.S. from 2011–2014. A total of 26 women with ICP and 27 control pregnancies with no prior history of gestational diabetes mellitus were recruited from outpatient antenatal services and followed until delivery. Alterations in glucose, incretins, cholesterol, and triglycerides were studied using a continuous glucose monitoring (CGM) system and/or a standard glucose tolerance test (GTT) in conjunction with GLP-1 and a fasting lipid profile. Fetal growth was quantified using adjusted birth centiles.

RESULTS

Maternal blood glucose concentrations were significantly increased in ICP during ambulatory CGM ($P < 0.005$) and following a GTT ($P < 0.005$). ICP is characterized by increased fasting triglycerides ($P < 0.005$) and reduced HDL cholesterol ($P < 0.005$), similar to changes observed in metabolic syndrome. The offspring of mothers with ICP had significantly larger customized birth weight centiles, adjusted for ethnicity, sex, and gestational age ($P < 0.005$).

CONCLUSIONS

ICP is associated with impaired glucose tolerance, dyslipidemia, and increased fetal growth. These findings may have implications regarding the future health of affected offspring.

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Received 8 September 2014 and accepted 7 November 2014.

Intrahepatic cholestasis of pregnancy (ICP) is the commonest liver-specific disorder of pregnancy. It affects 0.67% of pregnancies in the U.K. and is more common in women of Araucanian and South Asian origin (1). ICP may manifest as early as the first trimester, although it predominantly occurs after 30 weeks' gestation (2). Clinically it is characterized by maternal pruritus (in the absence of any dermatological disease) and raised serum bile acids (3). The incidence of adverse pregnancy outcomes including spontaneous preterm labor, meconium passage, fetal asphyxia, respiratory distress, and stillbirth have been reported to be significantly increased in pregnancies complicated with significantly elevated maternal serum bile acids (>40 μmol/L) (1–5).

Normal pregnancy has been shown to be mildly cholestatic (6,7). It is therefore likely that ICP occurs in some women who, despite normal gestational alterations in the relevant hepatic metabolic pathways, are unable to maintain adequate bile acid homeostasis. There is increasing evidence to support a role for the primary bile acid receptor farnesoid X receptor (FXR) in influencing lipid and glucose homeostasis in addition to the known effects upon bile acid metabolism (8–11). Women predisposed to gestational dysregulation of one of these pathways may also be at increased risk of a disorder in another. More recently, the G protein–coupled receptor TGR5 has also been identified as a bile acid receptor involved in promoting incretin release and energy homeostasis (12).

An association between glucose intolerance and dyslipidemia in ICP has previously been reported (5,13–16), with a recent retrospective study reporting an increased incidence of gestational diabetes mellitus (GDM) following the onset of cholestasis, suggesting that this may be the result of aberrant bile acid homeostasis (17).

The consequences of programming, by which a stimulus or insult at a sensitive period of early life may have a permanent and detrimental effect on the structure, physiology, or metabolism of the offspring, is now well accepted (18). There is also now increasing evidence to suggest accelerated fetal growth in pregnancy complicated by ICP (17) with reports of infants who are large for gestational age at birth (4,14). Although unconfirmed, it is possible that this may contribute to the metabolic changes reported in the adolescent offspring of cholestatic pregnancies (19).

A previous prospective study of 31 inpatients with ICP reported a significant increase in glucose excursions following oral glucose tolerance testing (GTT) and postprandially over a 24-h period (20). This prospective study was undertaken to further investigate the temporal association between ICP and alterations in maternal glucose and lipid homeostasis. In order to reduce some of the potential influence of hospital admission on glycemic control (e.g., as a consequence of reduced activity and a change in diet), temporal glucose concentrations were studied at home using a continuous glucose monitoring (CGM) system (CGMS).

The use of CGMS in pregnancy is now well accepted (21) and helps provide a more physiological insight into ambulatory maternal glycemic control.

RESEARCH DESIGN AND METHODS

This study was undertaken at two university maternity hospitals, Queen Charlotte's and Chelsea Hospital, London, U.K., and Women & Infants Hospital of Rhode Island, Providence, RI. Following approval from the National Research Ethics Service, London, U.K. (12/LO/0255) and Women & Infants Hospital of Rhode Island institutional review board (11-0063), a total of 53 women with a singleton pregnancy were recruited between February 2011 and February 2014: 26 with ICP and 27 with uncomplicated pregnancies. At enrollment, control subjects were matched for prepregnancy BMI (± 3.0 kg/m^2), maternal age (± 2 years), gestational age (± 2 weeks), and geographical location.

All cases of ICP were confirmed by demonstration of serum bile acids ≥10 μmol/L, raised liver transaminase enzymes in association with pruritus, and no additional identifiable cause for their liver dysfunction (3).

Exclusion criteria for ICP cases were other causes of hepatic dysfunction, including preeclampsia, the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), acute fatty liver of pregnancy, primary biliary cirrhosis, active viral hepatitis, and any ultrasound abnormality that may result in biliary obstruction. Exclusion criteria for control subjects were the same as those for case subjects.

Additional exclusion criteria included a history of previous gestational or preconception diabetes and current use of oral or intramuscular steroids, calcineurin inhibitors, or β-blockers. Patients with a history of Cushing syndrome, pheochromocytoma, acromegaly, bariatric surgery (gastric bypass), or active inflammatory bowel disease were also excluded.

Participants were fitted with a CGMS (iPro2; Medtronic) worn on the flank over 3 days. They were requested to eat three healthy meals a day (ad libitum) with little or no snacking between meals. The iPro was calibrated to a minimum of four capillary blood glucose readings (OneTouch Ultra2; LifeScan) taken immediately before each meal and prior to bed. The time at which each meal was taken was recorded on a diary card including a brief description of what was consumed. If CGM data were missing due to sensor failure or a calibration error, this was omitted from the analysis. In addition, in the event that a snack was recorded as having been eaten within 3 h of a meal, the corresponding glucose value was omitted from the analysis.

The level of physical activity between individuals was not standardized, but women were asked to wear a pedometer (Walking Style Pro; Omron Ltd) and to continue their normal daily routine.

The CGMS and capillary blood glucose data were uploaded to CareLink (Medtronic), a secure socket layer 128-bit encrypted server, and interpreted in accordance with recently published guidelines (21).

Following an overnight fast, bile acids, lipids, glucose, and alanine transaminase levels were assayed by colorimetery using the ARCHITECT *ci*16200 (Abbott Diagnostics) or Modular P analyzer (Roche), respectively, at the two study sites. Where available, plasma total GLP-1 concentrations were measured using an in-house radioimmunoassay (22), with an intra- and interassay variation of <10%.

Alterations in glucose homeostasis were assessed under standardized conditions using a 100-g oral GTT and the results compared with the Carpenter and Coustan criteria for the diagnosis of GDM (23).

Data concerning maternal age, BMI, ethnicity, smoking history, and parity were recorded. Gestational age was calculated with reference to the first

trimester dating scan. Birth weight centiles were calculated following adjustment for maternal BMI, parity, and ethnicity as well as infant sex and gestation using country-specific parameters (grow version 1.2.1.0 and 1.2.4.0; 2014). As there is no consensus in the current literature for the correct range of BMI to use for adjustment, we chose to correct for BMI ± 3 kg/m^2 prior to commencement of the study. Infants born small for gestational age (SGA) were defined as having an adjusted birth weight <10th centile. Similarly, infants born large for gestational age (LGA) were defined as having an adjusted birth weight >90th centile (24). Macrosomia was defined as a birth weight of >4.5 kg (14).

Statistical Analysis

Categorical variables were compared between ICP and control groups by Fisher exact test. Continuous and count variables were compared between groups by Student *t* test or the Mann–Whitney *U* test as appropriate. Continuous variables were graphed in each group to detect deviations from a normal distribution. Variables that were not normally distributed were summarized by medians and ranges and natural logarithm-transformed prior to regression. Multiple linear regression was used to adjust group mean differences for demographic and clinical variables. Age, parity, BMI, and calories were included in the models as continuous covariates. Changes in glucose parameters over time were examined by linear regression for longitudinal data. Compound heterogeneous symmetry was assumed for the within-patient correlation. Measurement time was included as a categorical variable, and study group by time interactions were assessed by a global F-test. Demographic and clinical covariates were included as described above. Categorical fetal outcome variables were adjusted for demographic and clinical factors by multiple logistic regression. Two-tailed *P* values are presented, with $P < 0.05$ considered statistically significant. *P* values were not adjusted for multiple comparisons.

RESULTS

The results of 26 women with ICP were compared with those from 27 women with uncomplicated pregnancies regarding alterations in blood glucose and lipid metabolism. There were no significant differences in the booking BMI, parity, racial group, or maternal or gestational age at recruitment between the two study groups (Table 1). In the ICP group, one woman smoked (six cigarettes a day), and two women had a previous history of viral hepatitis; however, both had normal synthetic liver function and enzymes prior to conception. Both the serum bile acids (33.1 ± 7.7 vs. 2.7 ± 0.4 μmol/L; $P \leq 0.005$) and alanine transaminase (121 ± 23.7 vs. 13.6 ± 1.2 IU; $P \leq 0.005$) were significantly higher in the ICP group compared with the control subjects. The mean gestational age at diagnosis of ICP was 32.9 weeks (± 1.1), with a mean gestational age at delivery of 37.4 weeks (± 0.3).

CGM

The ambulatory glycemic profile of 42 pregnant women (19 women with ICP and 23 control subjects) was assessed under nonstandardized conditions. The mean absolute difference of capillary glucose measurements compared with CGMS values in ICP and control subjects was 8.5% (± 0.6) and 9.8% (± 1.4), respectively, indicative of a good calibration. The blood glucose concentration over time was higher in women with ICP compared with uncomplicated pregnancy (Fig. 1), and this remained significantly elevated following adjustment for maternal age, BMI, parity, and ethnicity ($P < 0.005$). These observations reflect a significant increase in the postprandial blood glucose concentration after each meal.

Over the total study period, the mean maternal peak postprandial glucose concentrations were significantly higher in women with ICP compared with uncomplicated pregnancy (7.2 ± 0.1 vs. 6.4 ± 0.1 mmol/L; $P \leq 0.005$). Although average ambulatory energy expenditure recorded by the pedometer in women with ICP was lower than the control group (101.5 calories: range 33.3–232.0 vs. 151.8 calories: range 36.7–332.7; $P = 0.06$), the differences in overall blood glucose concentration between the two groups during the study period remained significantly higher in ICP, 5.5 (± 0.3 mmol/L) versus 5.1 (± 0.1 mmol/L), despite adjustment for maternal age, parity, calories, ethnicity, and BMI ($P = 0.028$).

GTT and Fasting Lipid Profiles

A total of 23 women with ICP and 24 women with uncomplicated pregnancies underwent GTT. Measurement of fasting and hourly postprandial blood glucose revealed a 30% incidence of GDM in ICP (7 of 23 vs. 0 of 24; $P \leq 0.005$). Prior to developing ICP, of these seven women, five had previously tested negative for GDM; the other two had early-onset cholestasis and tested positive <24 weeks gestation at the time of diagnosis. This was in conjunction with elevated blood glucose levels in women with ICP at 60, 120, and 180 min (Fig. 2*A*). In addition, there was a reduction in the level of plasma GLP-1 in ICP compared with uncomplicated pregnancy, with a significant reduction in plasma concentrations at 60 min following glucose ingestion. Subgroup analysis of GLP-1 serum levels in the ICP cohort suggested that treatment with ursodeoxycholic acid (UDCA) may have augmented GLP-1 secretion (Fig. 2*B*).

The lipid profiles of women with ICP showed significantly higher fasting total cholesterol, LDL cholesterol, and serum

Table 1—Maternal demographic details of 26 women with ICP and 27 with uncomplicated pregnancy (control subjects)

Demographic	ICP	Control	*P* value
Maternal age (years)	30.5 (± 1.1)	31.1 (± 1.0)	0.69
Gestation age at testing (weeks)	34.6 (± 0.6)	34.0 (± 0.8)	0.56
BMI (kg/m^2)	25.5 (± 1.0)	23.4 (± 0.5)	0.08
Parity	1.0 (0–7)	0.0 (0–2)	0.08
Racial group			
White	17 (65.4)	18 (66.7)	0.82
Hispanic	2 (7.7)	2 (7.4)	
Black	2 (7.7)	4 (14.8)	
Asian	5 (19.2)	3 (11.1)	

All data expressed as mean values (± SEM) with the exception of parity expressed as median (range) and racial group expressed as number and column percentage. Intergroup comparison was performed using Fisher exact test ($P = 0.82$).

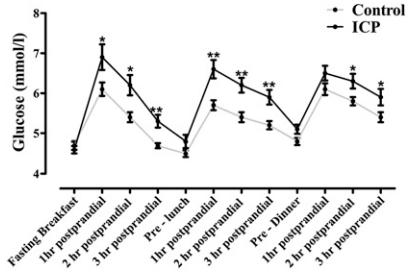

Figure 1—Glycemic profile at time of recruitment of women with ICP (n = 19) and uncomplicated pregnancy (n = 23) using a CGMS (Medtronic iPro2) over 3 days. Data analysis adjusted for maternal age, BMI, parity, and ethnicity and expressed as mean values ± SEM. Repeated-measures linear regression time by group interaction, $P \leq 0.005$. Intergroup comparisons at each time point. *$P \leq 0.05$; **$P \leq 0.005$.

triglycerides compared with uncomplicated pregnancy (Fig. 2*C*). In addition, HDL cholesterol was significantly reduced, with a corresponding increase in the total cholesterol/HDL ratio in ICP.

Treatment with UDCA did not appear to influence the concentration of glucose or lipids in the women with ICP (data not shown).

There was no significant difference in mean birth weight for singleton babies between the two groups (P = 0.54) (Table 2). However, adjusted birth weight centiles for babies born to women with ICP were significantly higher compared with those for babies born to women with uncomplicated pregnancy (Table 2). In addition, there were more LGA babies in ICP (P = 0.05) (Table 2).

CONCLUSIONS

This study is the first to use CGMS to compare maternal glucose levels in ICP with uncomplicated pregnancy and has shown that postprandial plasma glucose levels are higher in affected women than in those with uncomplicated pregnancy. Oral GTT revealed a 30% incidence of GDM in women with ICP, and this was associated with reduced plasma levels of GLP-1. This association was lost in women treated with UDCA. The findings of this prospective study support the observations made by ourselves and others that ICP is associated with increased rates of GDM (13,14,17) and characterized by elevated serum levels of glucose (20), triglycerides, and total and LDL cholesterol, as well as a fall in HDL cholesterol (15,16,25).

Bile Acids and Glucose and Lipid Homeostasis

There is now growing evidence to suggest that the rise in bile acids following a meal plays a role in regulation of postprandial changes in glucose, lipid, and energy homeostasis and that manipulation of this axis may prove effective in the treatment of metabolic syndrome (26,27).

The ICP-associated changes in glucose and lipid metabolism may potentially be explained by a reduction in the activity of the bile acid receptors FXR and TGR5, which are also involved in glucose and lipid metabolism (26,27). Pregnancies complicated by ICP are associated with a supraphysiological rise in sulfated progesterone metabolites (28); including the 3β-sulfated progesterone metabolite epiallopregnanolone sulfate, which has been shown to antagonize FXR (29).

Murine $fxr^{-/-}$ models are characterized by hypertriglyceridemia, impaired glucose, and insulin tolerance (8,30,31), with a reduction in whole-body glucose disposal during hyperinsulinemic-euglycemic clamp studies (30). Given that bile acid activation of FXR has been shown to attenuate gluconeogenesis (8,31,32) and induce expression of the insulin-regulated glucose transporter GLUT-4 (33), disruption in these homeostatic pathways may explain the rise in blood glucose observed in ICP. Furthermore, it is probable that the elevated levels of triglyceride may also contribute to peripheral insulin resistance within skeletal muscle tissue (8).

Bile acids have recently been reported to act synergistically with glucose to promote insulin release through FXR-mediated pathways (34–36). Enteric bile acids also stimulate TGR5, resulting in GLP-1 release and further stimulating pancreatic β-cell function (12,37,38). It is therefore probable that the insulinotropic effect of prandial bile acid release will be attenuated in ICP, both directly and indirectly, due to disruption of the enterohepatic circulation. In our study, the postprandial concentration of GLP-1 was significantly lower at 60 min in women with ICP; however, we observed that treatment with UDCA partially reversed this deficit. In support of this, a recent longitudinal study reported an increased GLP-1

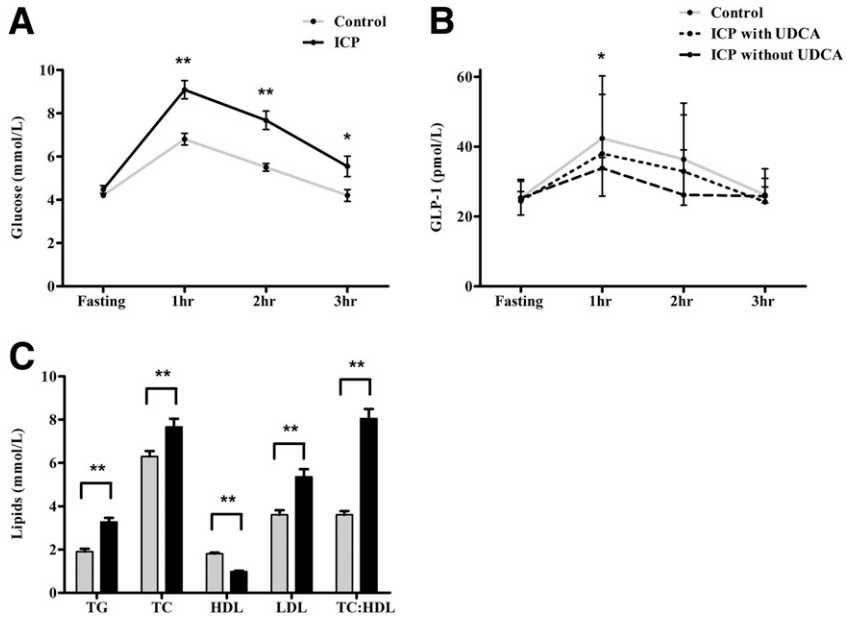

Figure 2—Fasting and postprandial blood results at time of recruitment from women with ICP and uncomplicated pregnancy. *A*: Serum glucose values following a 100-g glucose load (GTT) in ICP (n = 23) and control subjects (n = 24). Repeated-measures linear regression time by group interaction, $P \leq 0.005$. *B*: Plasma GLP-1 values following a GTT in ICP with UDCA (n = 9) or without UDCA (n = 6) and control subjects (n = 20). Repeated-measures linear regression on log GLP-1 values time by group interaction, P = 0.97. *C*: Fasting lipid profile in ICP (n = 26) and control subjects (n = 27). Glucose and lipid data expressed as mean values ± SEM. GLP-1 data expressed as median (25th and 75th interquartile range). Intergroup comparisons at each time point. *$P \leq 0.05$; **$P \leq 0.005$. TC, total cholesterol; TC:HDL, total cholesterol/HDL ratio; TG, triglyceride.

Table 2—Fetal outcome data of babies born to mothers with ICP and uncomplicated pregnancy (control subjects)

Fetal outcome	ICP	Control	*P* value
Infant sex			0.78
Male	15 (58)	14 (52)	
Female	11 (42)	13 (48)	
Gestation at delivery (weeks)	37.4 (± 0.3)	40.1 (± 0.3)	<0.005
Birth weight (g)	3,298 (± 106)	3,381 (± 84)	0.54
Adjusted birth centile*	69.9 (± 4.5)	36.1 (± 4.3)	<0.005
LGA*	6/26 (23)	1/27 (4)	0.05
Macrosomia	1/26 (4)	0/27 (0)	0.49

Infant sex expressed as absolute values (percentage) and additional data expressed as mean (± SEM). Macrosomia is birth weight >4,500 g. **P* values were adjusted for gestational age, BMI, parity, race, and infant sex.

release and a fall in plasma glucose levels following initiation of UDCA therapy (39).

The observation that ICP is associated with an increased incidence of GDM is consistent with the findings of others; however, in these studies, no indication was given regarding the gestational age at which either condition was diagnosed (5,13,14). Although one study has previously reported a temporal relationship between ICP and glucose intolerance, neither quantification of serum bile acid concentrations nor the incidence of GDM was undertaken (20). Our results from this prospective study suggest that the incidence of GDM increases following the onset of ICP, consistent with one previous retrospective series (17).

The changes in fasting triglyceride and LDL cholesterol measurements are consistent with those observed in nonpregnant $fxr^{-/-}$ mice (8,30,31). In contrast, the concentration of HDL cholesterol was reduced in ICP (15,16,25), a finding that is not seen in mice deficient in fxr. FXR stimulates expression of peroxisome proliferator–activated receptor-α (10), a nuclear receptor responsible for the regulation of expression of apolipoprotein A1, a major protein component of HDL (40). Interestingly, both the levels of HDL cholesterol and apolipoprotein A1 have been shown to fall in ICP with advancing gestation (15), possibly due to reproductive hormone-related antagonism of FXR. In agreement with a previous longitudinal study, analysis of the lipid profiles of UDCA-treated women with ICP did not differ significantly from those not receiving treatment (15).

ICP and Fetal Birth Weight

In keeping with Pedersen's hypothesis that elevated maternal glucose promotes hyperinsulinemia and fetal growth (41), adjusted birth weight centiles were significantly increased in pregnancies complicated by ICP. Several studies have demonstrated that ICP has a positive influence on fetal growth. A recent large population-based cohort study reported a significant increase in the incidence of LGA infants in pregnancies complicated by ICP even after controlling for diabetes and preeclampsia (14). These findings are consistent with a small retrospective study in which the incidence of LGA infants was higher compared with SGA infants (13) and another that reported increasing customized singleton birth weight centiles with advancing gestational age in cholestatic pregnancy (17). More recently, a prospective population-based case-control study reported a significant increase in the customized birth weight centiles as well as a lower incidence of SGA infants born to mothers with ICP compared with control subjects (4).

The HAPO Study (42) demonstrated a continuum of risk for maternal glucose levels and adverse pregnancy outcomes, with a strong association of birth weight above the 90th percentile and increasing maternal glycemia. Furthermore, elevated serum triglycerides have also been proposed to promote fetal growth independent of glucose levels (43), giving two biologically plausible explanations for the increase in fetal growth in ICP observed in this study.

ICP and Fetal Programming

The consequences of programming, by which a stimulus or insult at a sensitive period of early life may have a permanent and detrimental effect on the structure, physiology, or metabolism of the offspring, are now well accepted (18). Despite no difference in maternal BMI or fetal birth weight, a recent study looking at the metabolic characteristics of 16-year-old offspring of women whose pregnancy was complicated by ICP (without GDM) reported sex-specific differences in BMI, fat distribution, cholesterol, and insulin resistance (19). There is mounting evidence to suggest that GDM increases the risk of the offspring of developing diabetes, obesity, and metabolic syndrome in later life (44,45). Given the higher incidence of maternal impaired glucose tolerance observed in pregnancies complicated by ICP, this may provide an alternative explanation for the metabolic changes observed in the offspring of affected women.

Summary

We have demonstrated that ICP is characterized by glucose intolerance and dyslipidemia, consistent with the changes seen in the metabolic syndrome, in conjunction with enhanced fetal growth. GDM also occurs more commonly in pregnancies complicated by ICP. It is plausible that the mechanism underlying our findings is attenuated activity of the bile acid receptors FXR and TGR5, which resolves following the fall in sulfated progesterones and/or estrogens at delivery. Of concern is the potential influence that these changes may have on the long-term morbidity of the offspring of affected mothers. Given the growing evidence in support of an association between ICP and GDM, the authors advocate a low threshold for screening women with new-onset cholestasis for impaired glucose tolerance. Further work is required to help clarify which metabolic pathways are altered in ICP in order to better promote both maternal and fetal well-being.

Funding. The research was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London and at Imperial College London. The research was also funded by the Wellcome Trust, the Genesis Research Trust, U.K., and the Department of Obstetric Medicine at Women & Infants Hospital of Rhode Island, Providence, RI.

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. M.G.M., P.H.D., and C.W. designed the study, researched the data, and wrote the manuscript. C.R. undertook the statistical analysis. J.C., M.M., N.M.K., M.L.H., and R.M. researched the data. K.C. and R.P. contributed to the discussion. C.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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