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Intrahepatic cholestasis of pregnancy and associated adverse pregnancy and fetal outcomes: a 12-year population-based cohort study

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Objective To determine the risk for adverse pregnancy and fetal outcomes in intrahepatic cholestasis of pregnancy (ICP).

Design Population-based cohort study.

Setting Swedish Medical Birth Register (MBR) 1997–2009.

Population A total of 1 213 668 singleton deliveries.

Methods Linkage of Hospital Discharge Register for exposure (ICP; n = 5477) with MBR for covariates.

Main outcome measures Gestational diabetes, pre-eclampsia, prematurity, and stillbirth.

Results Intrahepatic cholestasis (ICP) was diagnosed in 0.32–0.58% of all pregnancies, with an increasing trend until 2005 ($P < 0.0001$). Compared with women who did not have ICP, women with ICP were more likely to have gestational diabetes (adjusted odds ratio, aOR, 2.81; 95% CI 2.32–3.41) and pre-eclampsia (aOR 2.62, 95% CI 2.32–2.78). Women with ICP were also more likely to have spontaneous (aOR 1.60, 95% CI 1.47–1.93) and iatrogenic (aOR 5.95, 95% CI 5.23–6.60) preterm delivery, with increased rates of induction of labour (aOR 11.76, 95% CI 11.04–11.62). However, this actively managed cohort of ICP cases was not at increased risk of stillbirth (aOR 0.92, 95% CI 0.52–1.62). Infants in ICP deliveries were more likely to have a low (<7) 5-minute Apgar score (aOR 1.45, 95% CI 1.14–1.85) and be large for gestational age at birth (aOR 2.27, 95% CI 2.02–2.55).

Conclusions Over time, a greater proportion of Swedish pregnant women have received a diagnosis of ICP, probably because of an increased awareness of the disorder. Our data confirm an increased risk of preterm delivery, but not of stillbirth, in actively managed ICP. The high rates of gestational diabetes and pre-eclampsia are new findings, and need to be considered in the management of ICP pregnancies.

Keywords Bile acids, gestational diabetes, intrahepatic cholestasis of pregnancy, intrauterine fetal death, obstetric cholestasis, pre-eclampsia, stillbirth, ursodeoxycholic acid.

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Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a common liver disease during pregnancy,[1] with reported incidence rates of between 0.4 and 15% in different countries and populations.[2,3] ICP is characterised by otherwise unexplained pruritus, with elevated bile acids and/or transaminases in the late second and third trimester of pregnancy. Pruritus spontaneously resolves and deranged liver function tests typically normalise within 4 weeks of delivery. Genetic predisposition (variants of hepatobiliary transport proteins), reproductive hormones, and environmental factors play key roles in the aetiology and pathogenesis of ICP.[2,3]

Initial observational studies, although limited in size, consistently found an association between ICP and adverse fetal outcome, including spontaneous preterm birth (12–44% of pregnancies), antenatal passage of meconium (16–58%), and fetal distress (10–44%) (comprehensively reviewed by Geenes

and Williamson).[3] Older studies on ICP in particular reported stillbirth rates of up to 15%, decreasing to 3.5% or less in more recent studies.[3] A large, prospective study performed in the west of Sweden during 1999–2002 demonstrated that adverse pregnancy outcome (i.e. spontaneous preterm labour, asphyxial events, and meconium staining of amniotic fluid, placenta and membranes) did not occur until maternal serum bile acids were >40 μmol/l.[4] This study only had 96 cases with serum bile acids above this level, so it was not large enough to establish whether severe ICP is associated with stillbirth. Furthermore, there are no studies in the current literature with sufficient numbers of ICP cases with maternal serum bile acids >40 μmol/l to answer this question.

The inconsistency of data on fetal risk can in part be attributed to unclear diagnostic criteria for ICP (increased bile acids/and or liver transaminases),[2,3] for example a lack of data on serum bile acid measurements. Historical studies described ICP as *icterus gravidarum*, but elevated bilirubin is a rare finding in ICP today.[5] Inconsistent findings may also be attributed to common, albeit unproven, changes in the management of ICP in the last two decades, for example the administration of ursodeoxycholic acid (UDCA) for relief from pruritus and biochemical reduction of maternal bile acids, as well as the induction of labour at 37 and 38 weeks of gestation, aiming to avoid stillbirth.[3] Thus, since the introduction of the tenth International Classification of Diseases (ICD-10) in 1997, the diagnosis, management, and outcome of ICP may have changed extensively.

In a nationwide cohort of more than 1.2 million singleton births in Sweden, between 1997 and 2009, we studied the prevalence of ICP and the association with adverse pregnancy and fetal outcome, taking maternal characteristics and year of birth into account.

Methods

Study participants

Through the Swedish Medical Birth Register (MBR) we identified 1 213 668 singleton deliveries occurring from the beginning of the year 1997 until the end of the year 2009. We excluded twins and higher multiples because they differ in fetal growth and duration of gestation, and have a higher occurrence of complications during pregnancy. Data from the Swedish MBR include information on about 98% of births in Sweden, with information on the mother as well as the pregnancy, delivery, and neonatal period. Data is prospectively collected, starting at the woman's first antenatal visit.

Exposure

We defined cases of ICP as those with the relevant ICD–10 code (O26.6) at discharge from the delivery hospital. ICD–10 coding was introduced in Sweden in 1997.

Covariates

Covariate data were obtained through the MBR, as previously described.[6] We classified maternal age at delivery into four groups: 13–24, 25–29, 30–34, and ≥35 years. Women were also categorised according to their antenatal body mass index (BMI, kg/m^2): lean (BMI ≤19.9), normal weight (20.0–24.9), overweight (25.0–29.9), or obese (≥30.0). Parity was classified into nulliparous or parous women. Cigarette smoking was recorded as none, 1–9 cigarettes daily, or ten or more cigarettes daily. The Swedish MBR also contains information on coexisting diseases such as diabetes mellitus and essential hypertension by checkbox and ICD–10 codes, and, in particular, the codes O14 and O15 for pre-eclampsia and O24.4 for gestational diabetes, respectively. Infants born small for gestational age (SGA) were defined as having birthweights of less than two standard deviations below the mean for gestational age and sex of the infant, according to a Swedish reference curve.[7]

Similarly, large for gestational age (LGA) was defined as a birthweight of more then two standard deviations above the mean for gestational age. Macrosomia was defined as a birthweight of 4500 g or more. A post-term pregnancy was defined as delivery at 42 weeks or more of gestation, and preterm birth was defined as delivery at <37 weeks of gestation, subclassified into moderate preterm birth (32 + 0 to 36 + 6 weeks of gestation) or very preterm birth (<32 weeks). Stillbirth was defined as fetal death after 28 weeks of gestation. A low Apgar score was defined as a score of <7 at 5 minutes. Neonatal death was defined as the death of an infant from 0 to 27 days after birth. The presence of meconium aspiration was obtained by diagnosis at discharge from delivery or neonatal care hospital (ICD–10: P24).

Using the unique personal identity number assigned to each citizen at birth or upon immigration,[8] we also linked data from the Swedish MBR with the Education Register through which we obtained information on the number of years of formal education completed as of 1 January 2010, categorised as ≤11 versus ≥12 years.

Statistical analysis

The main outcome measure was stillbirth. Secondary outcomes were gestational diabetes, pre-eclampsia, preterm birth (classified into spontaneous or iatrogenic), neonatal death, low Apgar score, meconium aspiration, LGA, macrosomia, SGA, and mode of onset of labour. Using logistic regression we estimated the risk of adverse pregnancy outcomes in relation to ICP by crude and adjusted odds ratios with 95% confidence intervals. Data were analysed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA). We compared women with a diagnosis of ICP with women with no such diagnosis, taking into account possible confounding factors

(maternal age, body mass index, parity, years of formal education, cigarette smoking, and calendar year of delivery). Because observations are not independent in women who delivered more than once during the study period, we calculated estimates using clustered data in the generalised estimation equation method (PROC GENMOD). Trends for rates of ICP diagnosis and stillbirth by calendar year of delivery were analysed in chi-square tests, which were also used for differences in maternal characteristics for women with and without ICP.

Results

Background data

A total of 1 213 668 singleton births between 1997 and 2009 were included in the cohort: among these were 5477 births to mothers with a diagnosis of ICP. ICP was diagnosed in 0.5% of all deliveries, with a significantly increasing trend from 1997 (0.32%) until 2005 (0.58%) ($P < 0.0001$), after which the prevalence stabilised (Figure 1).

Women with ICP were generally older and less likely to smoke cigarettes, or to be overweight or obese (BMI $\geq$ 25.0 kg/m^2), than women without ICP (Table 1). They more often had higher education and were more often born in the Nordic countries. Essential hypertension was more common in women with ICP (1.1 versus 0.6% in women without ICP), as was diabetes mellitus (1.3 versus 0.4%).

Pregnancy outcome and ICP

In the adjusted analysis, women with ICP had an increased risk of gestational diabetes (aOR 2.81, 95% CI 2.32–3.41) and pre-eclampsia (aOR 2.62, 95% CI 2.32–2.78), compared with women who did not have ICP (Table 2). There was no increased risk of antepartum bleeding or placental complications (aOR 0.78, 95% CI 0.56–1.07).

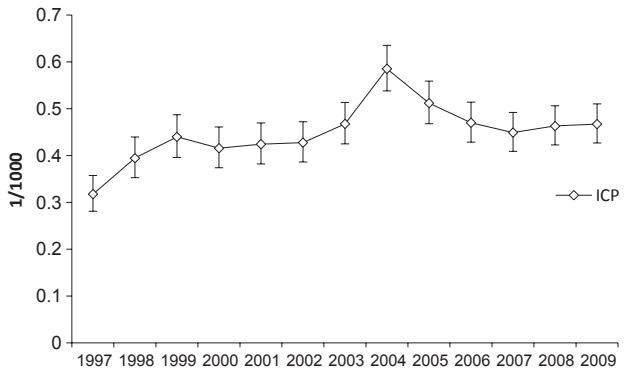

Figure 1. Prevalence of ICP in Sweden for the period 1997–2009. Error bars indicate the 95% confidence intervals.

Table 1. Maternal characteristics for singleton pregnancies with and without ICP in Sweden for the period 1997–2009

	ICP		No ICP		*P**
	n	Rate	*n*	Rate	
Total	5477	0.5	1 208 191	99.5	
Maternal age (years)					<0.0001
13–24	574	10.5	181 366	15.0	
25–29	1503	27.4	379 276	31.4	
30–34	2062	37.7	418 859	34.7	
≥35	1338	24.4	228 670	18.9	
Data missing	—	—	20	—	
Body mass index (kg/m^2)					<0.0001
≤19.9	486	10.4	105 509	10.0	
20.0–24.9	2676	57.0	572 175	54.1	
25.0–29.9	1093	23.3	265 094	25.1	
≥30.0	442	9.4	114 387	10.8	
Data missing	780	—	151 026	—	
Parity					0.98
0	2412	44.0	532 295	44.1	
≥1	3065	56.0	675 896	55.9	
Education					<0.0001
≤11	2441	45.7	626 029	53.1	
≥12	2906	54.4	552 718	46.9	
Data missing	130	—	29 444	—	
Country of birth					<0.0001
Nordic countries	4812	87.9	1 000 222	82.9	
Non-Nordic countries	662	12.1	206 464	17.1	
Data missing	3	—	1505	—	
Cigarette smoking					<0.0001
None	4739	94.3	1 026 132	90.3	
1–9	210	4.2	79 251	7.0	
≥10	78	1.6	31 487	2.8	
Data missing	450	—	71 321	—	
Essential hypertension					<0.0001
Yes	60	1.1	7167	0.6	
No	5417	98.9	1 201 024	99.4	
Diabetes mellitus					<0.0001
Yes	70	1.3	5269	0.4	
No	5407	98.7	1 202 922	99.6	

*ICP versus non-ICP, estimated by chi-square tests.

There was a strong association between ICP and moderate preterm birth (aOR 3.30, 95% CI 3.00–3.63), whereas the risk of very preterm birth was decreased (aOR 0.47, 95% CI 0.27–0.81). Women with ICP had a higher risk of undergoing caesarean section (aOR 1.26, 95% CI 1.13–1.33), which was confined to emergency caesarean section, whereas there was no associated risk for elective caesarean section (aOR 1.04, 95% CI 0.93–1.16). There was a strong association between ICP and induction of labour (aOR 11.76, 95% CI 11.04–12.52) (Figure 2). When we restricted the analysis to women with spontaneous onset of labour, the aOR for emergency caesarean section among women with ICP was 1.25 (95% CI 1.05–1.50).

Table 2. ICP and associated risks of adverse gestational outcomes

Pregnancy outcome	ICP		No ICP		Crude		Adjusted	
	n	Rate	*n*	Rate	OR	95% CI	OR*	95% CI
Gestational diabetes mellitus								
Yes	146	2.7	11 468	0.9	2.86	2.41–3.38	2.81	2.32–3.41
No	5331	97.3	1 196 723	99.1	1		1	
Pre-eclampsia								
Yes	364	6.7	33 539	2.8	2.49	2.23–2.78	2.62	2.32–2.78
No	5113	93.4	1 174 652	97.2	1		1	
Antepartum bleeding/placental complications								
Yes	56	1.0	13 642	1.1	0.90	0.69–1.18	0.78	0.57–1.07
No	5421	99.0	1 194 549	98.9	1		1	
Caesarean section**								
Yes	1068	19.6	187 604	15.6	1.30	1.23–1.32	1.26	1.13–1.33
No	4393	80.4	1 016 523	84.4	1		1	
Data missing	0	—	30	—	—	—	—	—
Very preterm birth (<31 + 6 weeks of gestation)**								
Yes	26	0.5	8404	0.7	0.68	0.46–1.00	0.47	0.27–0.81
No	5432	99.5	1 194 747	99.3	1		1	
Data missing	3	—	1006	—	—	—	—	—
Moderate preterm birth (32 + 0–36 + 6 weeks of gestation),*****								
Yes	695	12,8	51 026	4.3	3.29	3.03–3.57	3.30	3.00–3.63
No	4737	87.2	1 143 721	95.7	1		1	
Data missing	3	—	1006	—	—	—	—	—
Induction of labour**								
Yes	3055	56.6	124 869	10.5	11.11	10.51–11.74	11.76	11.04–12.52
No	2346	43.4	1 065 338	89.5	1		1	
Data missing	60		13 950					

*Odds ratios have been adjusted for maternal age, parity, BMI, years of education, cigarette smoking, and year of delivery.
**Only live births were included.
***The risk of delivering moderate preterm was calculated through a comparison with deliveries at 37 weeks and later.

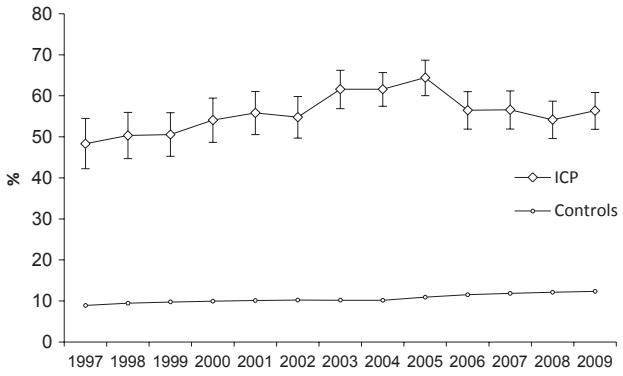

Figure 2. Induction of labour in women with and without ICP in Sweden for the period 1997–2009. Error bars indicate 95% confidence intervals, which are very narrow for controls.

We further categorised preterm birth, and found that the highest risk in women with ICP was found for iatrogenic preterm birth (aOR 5.95, 95% CI 5.23–6.60), whereas the risk for spontaneous preterm birth was only marginally increased (aOR 1.60, 95% CI 1.47–1.93). Women with ICP had a significantly reduced risk for post-term delivery (aOR 0.21, 95% CI 0.17–0.21).

Fetal outcome and ICP

The absolute number of stillbirths in cases of ICP varied from three to zero per year between 1997 and 2009 (Figure 3), and was not significantly increased (aOR 0.92, 95% CI 0.52–1.62) compared with women without this diagnosis. When the period from 1997 to 2005 was analysed separately for a possible trend, no statistical significance was found ($P = 0.26$). There were no significant increases in risk of neonatal death (aOR 0.45, 95% CI 0.15–1.40) or meconium aspiration (aOR 1.41, 95% CI 0.72–2.72) (Table 3); however, infants born to women with ICP were significantly more likely to have a low Apgar score (<7) at 5 minutes (aOR 1.45, 95% CI 1.14–1.85), and were more often LGA (aOR 2.27, 95% CI 2.02–2.55) (Table 3). When restricting the analysis to deliveries with a spontaneous

onset of labor, the aOR for Apgar score <7 at 5 minutes among women with ICP was 1.78 (95% CI 1.19–2.64). Excluding women with gestational diabetes did not influence the association between ICP and LGA babies (aOR 2.22, 95% CI 1.97–2.51).

Discussion

Main findings

This nationwide cohort study of ICP has two main findings. Firstly, ICP was strongly associated with gestational diabetes and pre-eclampsia. Secondly, women with ICP who were actively managed were not at an increased risk for stillbirth compared with women who did not have ICP.

Strengths and weaknesses

The main strength of this study is the large nationwide study population investigated over a time period of more than a decade, with modern active management, indicating an awareness of ICP among healthcare providers. The main weakness of this study is the lack of data on serum bile acid levels.

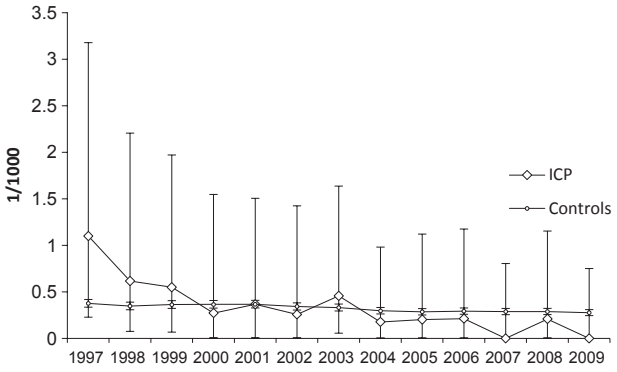

Figure 3. Rates of stillbirth in women with and without ICP in Sweden for the period 1997–2009. Error bars indicate 95% confidence intervals.

For the majority of the outcomes reported the adjusted odds ratios were increased, as compared with crude odds ratios, which is unusual, as associations are generally diluted in adjusted analyses. However, this depends on the distribution of confounding factors among exposed and unexposed pregnancies. Women with ICP were generally of older age,

Table 3. ICP and associated risks of adverse fetal outcome

Fetal outcome	ICP		No ICP		Crude		Adjusted	
	n	Rate	*n*	Rate	OR	95% CI	OR*	95% CI
Stillbirth								
Yes	16	0.3	3870	0.3	0.91	0.56–1.49	0.92	0.52–1.62
No	5461	99.7	1 204 321	99.7	1		1	
Apgar score <7 at 5 minute of age**								
Yes	77	1.4	12 925	1.1	1.32	1.05–1.65	1.45	1.14–1.85
No	5355	98.6	1 183 080	98.9	1		1	
Data missing	29	—	8 152	—	—	—	—	—
Neonatal death (0–27 days)**								
Yes	8	0.2	2058	0.2	0.86	0.43–1.72	0.45	0.15–1.40
No	5453	99.8	1 202 099	99.8	1		1	
Meconium aspiration**								
Yes	10	0.2	1729	0.1	1.28	0.68–2.37	1.41	0.72–2.72
No	5451	99.9	1 202 428	99.9	1		1	
Large for gestational age**								
Yes	426	7.8	44 537	3.7	2.20	1.99–2.44	2.27	2.02–2.55
No	5022	92.2	1 155 109	96.3	1		1	
Data missing	13	—	4511	—				
Macrosomia (birthweight ≥4500 g)**								
Yes	191	3.5	48 196	4.0	0.87	0.75–1.00	0.87	0.74–1.02
No	5257	96.5	1 152 138	96.0	1		1	
Data missing	13	—	3823	—	—	—	—	—
Small for gestational age**								
Yes	59	1.1	26 948	2.3	0.48	0.37–0.62	0.44	0.32–0.60
No	5389	98.9	1 172 698	97.7	1		1	
Data missing	13	—	4511	—	—	—	—	—

*Odds ratios have been adjusted for maternal age, parity, BMI, years of education, cigarette smoking, and year of delivery.
**Only live births were included.

which would lower the estimate in an adjusted compared with a crude analysis; however, women with ICP were less likely to be overweight and obese, and were less likely to smoke, which increases the adjusted odds ratio because of the association with the adverse outcome under study.

Interpretation

It has been suggested that the active management of ICP by the induction of labour before 38 weeks of gestation might decrease the incidence of stillbirth.[3] Indeed, we observed no increased risk of stillbirth in women with ICP during a period of active management, which is reflected by an 11–fold increased risk of induction of labour and a five-fold increased risk of iatrogenic preterm birth, which in turn resulted in lower rates of spontaneous preterm birth. This development may be attributed to an increased awareness in ICP that is reflected by the rising number of women with an ICP diagnosis until 2005, possibly influenced by a large observation and intervention study performed in the meantime.[4,5] We found an ICP incidence of 0.5%, which is, as expected, lower than in the prospective western Swedish study, where women were specifically asked about pruritus, and in which serum bile acids were measured up to four times each month.[4]

This is the first systematic description of a highly significant association of ICP with pre-eclampsia and gestational diabetes,[9,10] which are both common obstetric complications, diagnosed in 2–8% and 3–5% of pregnancies, respectively. Previously, the coexistence of ICP and gestational diabetes or pre-eclampsia had been reported as cases or small summaries only.[11–16] Indeed, these conditions were used as exclusion criteria in prospective ICP studies.[4,17]

Pre-eclampsia and gestational diabetes seem to share common pathogenetic pathways. A systemic review of chronic disease relevant to pregnancy revealed that pregnancy exaggerates atherogenic-like responses, including insulin resistance and dyslipidaemia, manifesting as pre-eclampsia and gestational diabetes.[18] Gestational diabetes and pre-eclampsia are more common in women who are overweight or obese;[19] however, in our cohort, women with ICP were less likely to have a high BMI. Consequently, overweight and obesity could not explain the association between ICP and these pregnancy-related diseases.

As elevated serum bile acids are the hallmark of ICP, one might speculate on their role in the pathogenesis not only of ICP but also of pre-eclampsia and gestational diabetes.[20] Recent animal studies have shown that bile acids, in addition to their well-established roles in dietary lipid absorption and cholesterol homeostasis, also act as signalling molecules, with systemic endocrine functions affecting glucose and lipid turnover and energy expenditure.[21,22] Furthermore, the taurine conjugate of UDCA restored glucose homeostasis in a mouse model of type-II diabetes mellitus,[23] and may improve liver and muscle tissue insulin sensitivity in men and women who are obese.[24] However, in light of these studies, it is difficult to assume that the elevated bile acid levels generally seen in ICP would reduce glucose tolerance to the extent found in gestational diabetes. At least in humans there is as yet no clear association of serum bile acid levels and metabolic syndrome/type-II diabetes mellitus.[25] Besides, bile acids are only a surrogate (and easier to measure) laboratory marker of ICP, which is more specifically characterised by abnormalities in progesterone metabolism.[26] For example, improvements of pruritus by treatment with UDCA were not correlated with improvements of serum bile acid levels but with changes in decreased progesterone disulphate excretion in urine.[27]

Nevertheless, it is surprising that the highly significant associations of ICP with pre-eclampsia or gestational diabetes have not been studied systematically before. One might speculate that the clinical conditions of pruritus and elevated bile acids, which are characteristic of ICP, led obstetricians to neglect elevation of liver function tests to be caused by preeclampsia, which is a major differential diagnosis of elevated liver function tests in pregnancy.[28] The interesting finding of an increased risk of LGA babies in ICP further strengthens the link between ICP and gestational diabetes, as LGA is a well-known complication in gestational diabetes;[10,23] however, the association between ICP and LGA remained after excluding women with gestational diabetes.

Conclusion

In conclusion, with modern active management there is an increased risk of moderate prematurity, but no increased risk of stillbirth, in ICP pregnancies. Our findings of a strong association of ICP with gestational diabetes and pre-eclampsia are novel, and are important to consider in the diagnostic procedure for women with ICP, and may optimise the clinical management. Further studies of ICP-related morbidity should focus on the possibly shared pathomechanism(s) leading to pre-eclampsia and gestational diabetes.

Disclosure of interests

None to declare.

Contribution to authorship

All authors performed literature searches, and wrote and edited the article. HUM initiated the project and provided metabolism and hepatology expertise, EWS and OS provided obstetric expertise, JFL and OS performed data collection and analysis, and provided epidemiological expertise.

Details of ethical approval

The study was approved by the Ethics Committee at Karolinska Institutet: 31 April 2008; ref. no. 2008/1182-31/4.

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