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Intrahepatic cholestasis of pregnancy is not associated with stillbirth in an Australian maternity population

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Dear Editor,

We read with interest the paper by Martineau and colleagues on intrahepatic cholestasis of pregnancy (ICP) published online on January 7 2014 (1). We have also investigated pregnancy outcomes for women with ICP among 975,240 maternities in New South Wales (NSW), Australia. However unlike Martineau we did not find an increased risk of stillbirth.

Briefly, we conducted a cohort study of all births of at least 20 weeks gestation or 400g birthweight (n=975,240) in NSW between 2001 and 2011, using linked routinely collected population health data from perinatal and hospital discharge data collections. ICP was identified in antenatal and birth hospital admission records by the diagnostic code O26.6 as classified in the International Classification of Diseases, 10th edition, Australian Modification. Logistic regression was used to calculate adjusted odds ratios for the association between maternal characteristics and pregnancy outcomes with ICP, with adjustment for age, plurality, parity, country of birth, maternal smoking in pregnancy, hospital maternity service level, pregnancy hypertension (gestational hypertension, preeclampsia or eclampsia) and gestational diabetes. These characteristics and outcomes have been validated against medical records and generally have high positive predictive values.

ICP was diagnosed in 1870 maternities, including 1758 (0.19%) singleton maternities and 112 (0.73%) multiple (twins, triplets and quadruplets) maternities, giving an average incidence rate of 190 ICP diagnoses per 100,000 maternities. Women with ICP were more likely than women without ICP to be older (OR 1.14, 95% CI 0.91-1.43 for women ≥ 40 years), of high parity (OR 1.36, 95% CI 1.17-1.59 for parity ≥3 versus parity 1), smoke in pregnancy (OR 2.00, 95% CI 1.79-2.25), have a multiple gestation (OR 3.47, 95% CI 2.86-4.21), and have gestational diabetes (OR 1.77, 95% CI 1.08-2.90, OR 1.70, 95% CI 1.45-1.99 respectively) or pregnancy hypertension (OR 2.09, 95% CI 1.84-2.38) ($p<0.0001$ for all characteristics).

There was no evidence for a difference in the odds of stillbirth (OR 0.72, 95% CI 0.40-1.31, p=0.28). However, there was strong evidence of the active management of ICP (Table 1), indicated by the higher odds of induction of labour (OR 3.12, 95% CI 2.84-3.42), caesarean section (OR 1.18, 95% CI 1.06-1.31) and planned preterm birth (OR 12.64, 95% CI 10.69-14.93). In addition, our study provides further evidence that ICP is associated with gestational diabetes (OR 1.70, 95% CI 1.45-1.99), pregnancy hypertension, spontaneous preterm birth and postpartum haemorrhage (1, 2).

Consistent with other studies (2-4) conducted in the era of active management of ICP but in contrast to Martineau's case-control study (1), we found no increased risk of stillbirth in women diagnosed with ICP. However as we did not have data on serum bile acid levels, we could not determine ICP severity. It has recently been reported that amongst women with severe ICP (serum bile acid ≥40μmol/L) , there was a 3-fold increased risk of stillbirth despite active management (5). As there were only 3 stillbirths recorded in the 143 cases of ICP diagnosed in women in Martineau's study (1), compared to 11 stillbirths in 1870 ICP-affected maternities in the current study, it is possible that the apparent increased risk of stillbirth despite active management of ICP reflects a chance finding due to small numbers rather than a true increased risk of stillbirth. Alternatively, there may be a higher prevalence of severe ICP in this population.

References

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Table 1: Pregnancy outcomes associated with intrahepatic cholestasis of pregnancy (ICP) in 975,240 maternities in NSW, Australia, 2001-2011

Pregnancy outcome	ICP (%)	No ICP (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)	p-value
Planned birth					<0.001
Spontaneous preterm	140 (7.5)	36156 (3.7)	6.02 (4.94 - 7.33)	4.76 (3.89 - 5.83)	
Planned preterm	313 (16.7)	27541 (2.8)	17.66 (15.14 - 20.61)	12.64 (10.69 - 14.93)	
Spontaneous term	338 (18.1)	525309 (54.0)	Ref	Ref	
Planned term	1079 (57.7)	384218 (39.5)	4.37 (3.86 - 4.93)	4.42 (3.90 - 3.5.01)	
Induction of Labour					<.0001
No	922 (49.3)	736425 (75.7)	Ref	Ref	
Yes	948 (50.7)	236799 (24.3)	3.20 (2.92 - 3.5)	3.12 (2.84 - 3.42)	
Mode of delivery					0.0005
Normal vaginal	1046 (56.0)	588998 (60.5)	Ref	Ref	
Instrumental	173 (9.3)	108347 (11.1)	0.90 (0.77 - 1.06)	0.89 (0.75 - 1.05)	
Caesarean section	650 (34.8)	275656 (28.3)	1.33 (1.2 - 1.47)	1.18 (1.06 - 1.31)	
Post partum haemorrhage					0.0025
No	1678 (89.7)	900762 (92.6)	Ref	Ref	
Yes	192 (10.3)	72319 (7.4)	1.43 (1.23 - 1.66)	1.26 (1.09 - 1.47)	
Stillbirth					0.28
No	1857 (99.4)	967060 (99.4)	Ref	Ref	
Yes	11 (0.6)	5838 (0.6)	0.98 (0.54 - 1.78)	0.72 (0.40 - 1.31)	
Gestational age					<.0001
<37 weeks	453 (24.2)	909663 (93.5)	4.57 (4.11 - 5.08)	3.20 (2.84 - 3.59)	
≥37 weeks	1417 (75.8)	63707 (6.5)	Ref	Ref	
Size for gestational age					0.57
SGA	193 (10.3)	91356 (9.4)	1.12 (0.96 - 1.3)	0.98 (0.84 - 1.14)	
LGA	210 (11.2)	103661 (10.7)	1.08 (0.93 - 1.24)	1.08 (0.93 - 1.25)	
AGA	1466 (78.4)	777587 (80.0)	Ref	Ref	
5 minute Apgar score					0.07
<7	62 (3.3)	20883 (2.2)	1.56 (1.21 - 2.02)	1.27 (0.98 - 1.63)	
≥7	1808 (96.7)	952487 (97.9)	Ref	Ref	

*Adjusted odds ratios for the association between intrahepatic cholestasis of pregnancy (ICP) were adjusted for age, plurality (singleton versus multiple), parity, country of birth, maternal smoking in pregnancy, maternal hypertension (chronic or gestational) and maternal diabetes (pre-existing or gestational).