Reviewer's report

Title: Maternal and neonatal risk factors for childhood type 1 diabetes: a matched case-control study

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Reviewer: Chris Patterson

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Minor Essential Revisions

1 Introduction

a) There are two recent publications describing meta analyses for maternal age and birth weight (Cardwell et al, Diabetes 2009 and Cardwell et al, Diabetologia 2010) which could usefully be cited and summarised somewhere in the manuscript. Together with the Caesarean section meta analysis (reference 11), these indicate that perinatal risk factors show significant but only rather modest associations with childhood type 1 diabetes.

2 Methods

a) Among the 611 cases a surprisingly large number (241 or ~40%) were excluded as 'outwith AMH'. The authors should document these exclusions in greater detail. How many were:
  • born outside the time period 1972-2002?
  • Home deliveries?
  • Resident in Aberdeen but delivered in a different hospital?
  • Inward migrants who were born outside Aberdeen?

Was any attempt made to include outward migrants (cases diagnosed in other parts of Scotland but born in Aberdeen) which, judging from the ~40% above, may have been quite numerous but could have been identified in the SSGCYD register and included in the study? Migrants are typically not representative of the population as a whole, so this is a potential source of bias which might have been overcome to some degree by ensuring that selected controls were also still resident in the Aberdeen area when the case was diagnosed.

b) The methodology used for estimating sample size in a matched case-control design should be cited. The power calculation assumes 10% of births in controls have maternal age >35 yr versus 20% in cases, giving an odds ratio of 2.25. This is rather unrealistically large since the best evidence available from meta-analysis (Cardwell et al, Diabetes 2009) estimates an odds ratio of only 1.10 (95%CI 1.01-1.20) for this >35 yr group relative to 25-29 yr group.

The use of subgroup analyses to compare the risk factors for early (<5 years) and later onset (5-14 years) type 1 diabetes is not ideal, and instead tests for
interaction in the logistic model should be used.

3 Results

a) Table 1 seems unnecessary since the information in the top half is included in Table 2, and most of the variables in the bottom half have a trivial number of missing values that need hardly be documented. Perhaps the main points in Table 1 could be stated in a sentence near the start of the Results.

b) Para 4 states ‘After adjusting for ..., the overall association between maternal smoking and type 1 diabetes was no longer significant (P=0.13). However, there was a suggestion of a reduced risk ..., with an adjusted OR of 0.67 with 95% CI (0.45, 0.99).’ Judging by this 95%CI not including 1.00, is this adjusted odds ratio not significant (i.e. P<0.05 rather than P=0.13)? The latter P value seems to be from a test which also includes the Unknown group (Table 2).

c) In Table 2 the ‘No (reference category)’ for Previous abortions is missing. Also in the Mode of Delivery there is no entry to show n(%) for CS. The section comparing Elective and Emergency CS is rather difficult to interpret; unlike all other analyses in the table it does not include all subjects. Instead both ought to be compared using either SVD or no CS as reference category.

4 Discussion

a) The only positive finding is of an inverse association between type 1 diabetes and maternal smoking, particularly for those diagnosed at older ages, does seems to have some support in the literature albeit from studies where the design may not be perfect. However, some additional consideration should be given in the Discussion to the possible bias through omission from the study of outward migrants, especially if large in number. Also, given the rather large number of statistical tests performed (~20 unadjusted analyses in Tables 2 and 3), there must be some possibility that this result is a type 1 error.

b) The authors should include some mention about the possible lack of power of their study to identify the sorts of small differences currently being described in meta analyses of perinatal risk factors. So, for example, this is a likely explanation for failure of their study to confirm the Caesarean section association (para 7) as significant. The authors' finding of an OR=1.16 (95%CI 0.82,1.66) is actually completely consistent with the meta analysis findings of a 20% increase in risk.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
'I declare that I have no competing interests'