Reviewer's report

Title: Do intrauterine or genetic influences explain the foetal origins of chronic disease? A novel experimental method for disentangling effects.

Version: 1 Date: 8 March 2007

Reviewer: Alan Taylor

Reviewer's report:

General
This is an interesting and well written article on a utilising a "natural experiment" to disentangle the genetic and intrauterine environment causes of chronic disease. I have some concerns about the article as it currently stands but I hope these can be easily addressed by the authors.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

My main concern with this article is that I think the authors should provide more details to allow the reader to establish the practicality of this research design.

In particular:

- It would be useful to have a discussion of the types and rates of disorder that could be studied by this design. Are the demographics of this somewhat unusual sample likely to reduce the rates of disorder in childhood/adulthood to levels too low to study effectively?

- No discussion is made of the issue of following up the sample until same useful medical "end point" can be measured. This would seem to be a very necessary consideration.

- Is there any data available on the "equivalence" of IVF and normally conceived children that would lend some weight to the validity of generalising from this sample? Its a pity that no preliminary assessment has been made of the children (who are 5-9) as this would make for a very useful addition here.

- An explicit discussion of how data will be analysed would also be a very useful addition. I think the current discussion of table 2 could be simply reworked to make this clearer. I assume that the homologous IVF and sperm donation groups will be combined and compared with the three remaining groups on some outcome, such as ADHD scores or diagnosis. Differences between these groups being used to infer true environmental causation?

- Based on the expected number of cases (table 1) it should then be relatively easy to provide some power estimates for these comparisons for various effect sizes. My rough calculations tell me that this is a well powered study which should be able to detect moderate sized effects (in means and odds ratios). This this is an important point to make in the article and can be addressed now rather than indicating it as a point for further study in the discussion. It also looks to me that the study would be adequately powered even if the potentially atypical surrogacy group were excluded.

- It would be useful to have an indication of how many pregnancies resulted in multiple births as this not explicitly mentioned.

- It is also unclear what the true useable expected sample sizes are given the response rates: 90% interest in further research and b) 84% agreement to access antenatal records. I would suggest an additional column to table 1 which would give the estimated final - useable sample sizes based on these rates of response.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author
The authors report that the level of agreement between maternal report and antenatal notes is "excellent". I think a little more accuracy is required.

In the last paragraph of the conclusion there is a reference error - should be [25] and not [24].

It is unclear how the expected sample sizes in Table 1 are calculated. The expected sample size for the homologous IVF group is less than the current sample size - I assume this is an error.

What is the total N in table 3.

I suggest changing the table 2 column label to Genetic "relationship - "other-offspring"" to help the reader

Discretionary Revisions (which the author can choose to ignore)

**Which journal?**: Appropriate or potentially appropriate for BMC Medicine: an article of importance in its field

**What next?**: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Quality of written English**: Acceptable

**Statistical review**: No

**Declaration of competing interests**: I have provided statistical advice to a colleague who has co-authored an article with Dr Thapar. This article is in review at this time. I am therefore a named author on this article.