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: 1 March 2007

Reviewer: Anastasia Iliadou

Reviewer's report:

General
The authors are presenting a novel approach to disentangle intrauterine effects from the effects of common genes with regard to an association between a risk factor (i.e. birth weight) and an outcome (i.e. ADHD). Although I believe this is an interesting way of trying to solve the mysteries of genetic confounding versus intrauterine effects for the developmental origins of adult disease, I believe that their approach needs more thinking and an extensive description.

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

My major comments are:

1) Table 2 seems rather confusing and a bit misleading. They describe their method as follows: If there is an environmental mediation you would expect to see an association in all 5 groups of IVF. If the association is genetically mediated then you would only find an association in those who are genetically related, which according to table 2 are only the homologous IVF and the sperm donation group.

If they do find an association in all 5 groups, environmental factors certainly play a role. However, genetic effects may still be present and be overridden by environmental factors (except for in the embryo donation group). So the question whether genes or intrauterine environment lies behind existing associations will still remain unclear.

If for example, there is a genetic mediation of the association between birth weight and risk of ADHD, wouldn’t you expect to see it in other groups as well and not just the homologous and sperm donation groups? In my opinion you would see it in the last group of “gestational surrogacy”, since the child is genetically related to the parents, but also in the egg donation group since the child has the sperm with its genetic content inherited from the father.

The genetic mediation part is more complicated than stated in table 2, hence a detailed description is highly relevant. In a pregnancy we can talk about maternal genetic effects and paternal genetic effects. Perhaps it will become clearer if they define the genetic mediation more carefully. One way is perhaps the following (and this is just a suggestion):

IVF Maternal genes Paternal genes Environment
Homologous Y Y Y
Sperm donation Y N Y
Egg donation N Y Y
Embryo donation N N Y
Surrogacy Y Y Y *
* Note: should be “No” for intrauterine environment related to the genetically related mother.

2) I also believe that in order to disentangle genetics from environment they need to describe in detail which groups to compare and what the conclusions would be depending on what groups they compare. It will make their approach clearer. For example comparing the 4 groups (homologous, sperm, egg and surrogacy) against the embryo group would at least give them a hint of whether genes are important or not, since in the embryo group the parents are not genetically related with the child. The importance of intrauterine environment could possibly be resolved by comparing the first 4 groups against the surrogacy group, where the intrauterine environment is provided by a surrogate mother.
3) In the 1st paragraph in the results section you mentioned that you gathered 722 families to date, but in table 1 the numbers do not add up to 722 (total in table 1 = 716), what was the missingness due to? Also state in the text what the expected numbers in Table 1 are based upon.

4) Please give a descriptive table of child characteristics (including number of twins, birth weight and gestational age distribution) and mother characteristics. A detailed description of your sample would be an asset to this manuscript.

5) Page 10, first paragraph, “However, such designs can not separate prenatal environment from inherited genetic influences on outcomes”. This sentence is referring to twin studies and is somehow misleading. Twin studies can separate genes from shared environment better than any design mentioned so far. By investigating associations stratified by zygosity you can either fully control for genes (in MZ) or partially control for genes in DZ (see for example reference by Morley R & Dwyer T Studies of twins: what can they tell us about the fetal origins of adult disease? Paediatr Perinat Epidemiol. 2005)

6) Please discuss also in a paragraph more about the generalisability and other limitations of your proposed approach. IFV has been extensively studied and reports have shown that maternal characteristics are significantly different from the rest of the population. In addition, even if you take those maternal differences into account, IVF pregnancies have more complications and a poorer pregnancy outcome, which can have implications for studying the fetal programming with your approach (see references by Kallen B et al., In vitro fertilization in Sweden: maternal characteristics, Acta Obstet Gynecol Scand. 2005 AND In vitro fertilization in Sweden: obstetric characteristics, maternal morbidity and mortality, BJOG. 2005). Moreover, given the interest in associations between birth weight and subsequent health, the high proportion (indicated in table 3) of twins may be difficult to handle. It is known that twins have lower birth weight and shorter gestational age compared to singletons, and rates of twinning may also differ between the proposed groups in your manuscript. Another limitation is of course the feasibility of these kinds of studies and whether they will have power enough to resolve research questions of interest.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Minor comments:

1. Abstract: You refer to your approach as a natural experimental design. I would be hesitant to call IFV as a “natural” approach. Although it is a great tool helping a lot of infertile couples, it seems rather “unnatural” and man made.
2. In the results section please state the actual numbers and the frequencies in parenthesis.
3. Page 10, first paragraph, Reference 24 should be reference nr 25 and I think you need to delete reference 24 since I do not recognize its purpose.
4. Regarding references:
   a. Ref nr 8. Should be Seckl JR and Meaney CJL
   b. Ref nr 10. The full title is: Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis.
   c. Ref nr12. The full title is: Effects of antenatal stress and anxiety: Implications for development and psychiatry.
   d. Ref nr 21. The full title is: Assisted reproductive technology in Europe, 1999. Results generated from European registers by ESHRE.

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 declare that I have no competing interests.