Neuromotor, cognitive, language and behavioural outcome in children born following IVF or ICSI: a systematic review

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CRD summary
The authors concluded that no increased risk of neurodevelopmental problems was found in children born following in vitro fertilisation or intracytoplasmic sperm injection. But, further good-quality longer-term research was required. There were some limitations to this review, but overall the authors’ conclusions reflected the evidence presented. The need for further longer-term research was justified in the text.

Authors' objectives
To evaluate neurodevelopmental outcomes in children born following in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI).

Searching
MEDLINE, EMBASE, PsycINFO and The Cochrane Library were searched for studies published in English between 1978 and December 2007. Search terms were reported. Reference lists of identified studies and reviews were screened.

Study selection
Studies that evaluated neurodevelopmental outcomes in children born following IVF or ICSI compared with a naturally conceived group of children were eligible for inclusion. Studies had to include 25 or more children in each group, follow-up children beyond the neonatal period and include less than 10 per cent of children born following ovulation induction only (without IVF or ICSI). The natural conception group had to exclude children born from donor gametes, adopted children and surrogate-born children. The review assessed different types of neurodevelopmental outcomes (neuromotor handicap, cognition, language and behaviour). Studies assessed outcomes in infant, pre-school and school age children. The included studies were prospective and retrospective controlled studies and register-based studies.

The authors stated neither how papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed internal validity (prospective cohort or register-based, four or more confounders accounted for, post-natal attrition 10 per cent or less, use of neurodevelopmental test with good validity and blinded outcome assessment) and external validity (internal validity, sample size and power to assess neurodevelopmental outcome). Discrepancies were resolved through consensus. Studies were classified as retrospective or prospective according to the timing of enrollment of the control group; studies which did not clearly state recruitment of all IVF/ICSI children in a region or centre were classified as retrospective. Attrition due to perinatal mortality was not taken into account. Details of scoring systems for validity were reported.

Data extraction
Two reviewers independently extracted data and resolved discrepancies through consensus.

Methods of synthesis
Only good quality studies were included in the narrative synthesis (criteria used to determine good quality were described). Register-based studies and controlled studies were discussed separately. Studies were grouped by age of child at assessment and type of neurodevelopmental outcome assessed.

Results of the review
Fifty-nine studies were included. Sample size ranged from 26 to 16,280. There was considerable overlap of children between studies.

Twenty-three studies were considered to have good internal and external validity and were included in the synthesis.
These included nine register-based studies and 14 controlled studies.

Register-based studies
Two of three studies that assessed the risk of cerebral palsy (CP) in children aged at least 1.5 to 2 years reported an increased risk among IVF/ICSI children. The increased risk disappeared when only singletons were analysed. The third study reported a similar risk in both groups. Four studies that also included younger children reported that the possible increased risk of CP in IVF/ICSI children generally disappeared after adjustment for important confounders. Two studies reported that the increased risk of epilepsy/convulsions remained after adjustment.

Five out of nine studies found no association between IVF/ICSI and mental retardation. Speech and language retardation was assessed in one study, which found no difference between IVF/ICSI children and naturally conceived children. Three of four studies reported no difference in behaviour. One study reported a reduction in developmental autism in IVF/ICSI children.

Controlled studies
Follow-up in infancy (nine studies including four that examined the same group of children): four of six studies assessing neuromotor development reported no difference between groups; one study reported poorer hand-eye co-ordination in IVF/ICSI children; and the other reported better psychomotor development in the IVF/ICSI group.

Five of six studies assessing cognition reported no difference between groups. One study reported lower developmental scores in IVF/ICSI children. Two of three studies assessing speech and language reported no difference between groups. Results were inconsistent among different speech and language outcomes in the third study. Six studies evaluated behaviour, but four studies involved the same group of children at different ages: these four studies and two other studies generally showed little difference between groups.

Follow-up of pre-school children (two studies): one study reported no difference between groups in neurological handicap or cognition; the other study reported that a difference in cognitive development between ICSI and IVF/naturally conceived children at 18 months was no longer present at five years.

Follow-up of school-age children (three studies): one study generally reported no differences between IVF/ICSI children and controls, but reported more psychological and behaviour problems in IVF children. Two studies reported no difference between groups in neuromotor development, but lower IQ in singletons born after ICSI compared with naturally conceived children.

Authors' conclusions
No increased risk of neurodevelopmental problems was found in IVF/ICSI children, but further good-quality research with longer term-follow-up was required.

CRD commentary
The review question was stated clearly and appropriate inclusion criteria were specified. Several relevant sources were searched, but no attempts were made to minimise publication or language bias. Appropriate methods were used to minimise reviewer error and bias during data extraction and validity assessment, but it was not clear whether similar steps were taken in study selection. Validity was assessed using specified criteria and results were reported. In view of the differences between studies, a narrative synthesis that only included the higher quality studies was appropriate.

Despite some limitations to this review, the authors’ conclusions reflected the evidence presented. The need for further longer-term research was justified in the text.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that there was a need for good-quality long-term research (registry-based or prospective studies) that carefully followed up all consecutive pregnancies in a hospital/fertility clinic and their naturally conceived controls. Ideally, follow-up would continue into adulthood. Future studies should also examine the effect of gender on...
outcomes. There was also a need to follow-up children born after cryopreservation of embryos, perimplantation genetic screening and in vitro maturation.

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