Neurodevelopmental outcome of children born following assisted reproductive technology

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Summary & Samenvatting

SUMMARY

Chapter 1. General introduction

The number of children born following assisted reproductive technology (ART) has shown a steady rise during the last decades. As a consequence of the growing number of children born after ART, health and development of these children has become of general importance. In this thesis the neurodevelopmental outcome of children born after ART is evaluated up to the age of two years. An attempt is made to unravel the biological mechanisms that may underlie potentially poorer neurodevelopmental outcome. The thesis is divided into 4 parts.

Part I; Overview of the literature

Chapter 2 contains a systematic review of studies which compare children born following IVF/ICSI to children born after natural conception by assessing outcome in terms of neuromotor development, cognition, speech/language and behaviour. Specific attention is paid to the studies' methodological quality based on study design, attrition, blinding of the assessor, validity of the neurodevelopmental tests used, confounders included and group size or power analysis. Twenty-three out of 59 studies had a good methodological quality including 9 register-based and 14 controlled studies. The register-based studies suggested that IVF/ICSI *per se* does not increase the risk for severe cognitive impairment (i.e. mental retardation) or neuromotor handicaps such as cerebral palsy (CP), the association of IVF/ICSI and CP being brought about by the association of assisted conception with risk factors, like preterm birth. In general, controlled studies of good quality did not report an excess of neurodevelopmental disorders in IVF/ICSI-children. However, the majority of studies followed the children during infancy only, thereby precluding pertinent conclusions on the risk of neurodevelopmental disorders that come to the expression at older ages, such as fine manipulative disability or dyslexia. Currently, a negative effect of assisted conception on the developing human brain has not been identified; however, further research of high methodological quality in children beyond pre-school age is needed.

Part II: The Groningen ART-cohort study

We investigated the effect of ovarian hyperstimulation and the in vitro procedure on neurodevelopmental outcome in cohorts of children born following conventional COH-IVF, MNC-IVF and NC children born to subfertile parents.

In **chapter 3**, we evaluated specific effects of ovarian hyperstimulation, the in vitro procedure, and a history of subfertility on neuromotor development at 3 months of age. Participants were 68 singletons born after COH-IVF, 57 singletons

born after MNC-IVF, and 90 NC singletons born to subfertile couples. To study the effect of subfertility itself, data from a fertile reference population (n = 450) were used. Early neuromotor development was measured by means of the quality of General Movements at 2 weeks and 3 months. Quality of general movements (GMs) may be classified as normal-optimal, normal-suboptimal, mildly abnormal, or definitely abnormal. Definitely abnormal GMs indicate brain dysfunction, mildly abnormal GMs normal but non-optimal brain function. Mildly abnormal and definitely abnormal GMs were observed equally frequently in COH-IVF, MNC-IVF, and NC singletons. But the three subfertile groups showed more mildly abnormal GMs than the reference population. This suggests that factors associated with subfertility rather than those related to IVF procedures may be associated with less-optimal early neurodevelopmental outcome.

Chapter 4 documents the neurological condition of the Groningen ART-cohort children measured with the Touwen Infant Neurological Investigation (TINE) at 4 and 10 months and the Hempel examination at 18 months. Both measures, TINE and Hempel, focus on the occurrence of minor neurological dysfunction. Due to the growing number of children born following assisted reproduction technology, even subtle changes in the children's health and development are of importance to society at large. Neurological examination resulted in a neurological optimality score (NOS), a fluency score and a clinical neurological classification. Fluency of movements is easily affected by neurological dysfunction and is therefore a sensitive measure for minimal changes in neuromotor development. The NOS and the fluency score were similar in COH-IVF, MNC-IVF and NC children. None of the children showed major neurological dysfunction and rates of minor neurological dysfunction at the three ages were not different between the three conception groups. In conclusion, we found no effects of ovarian hyperstimulation or the in vitro procedure itself on neurological outcome in children aged 4-18 months.

Chapter 5 evaluates the neurological condition of the Groningen ART-cohort children with the Hempel examination at 2 years. Besides the effects of ovarian hyperstimulation and the IVF laboratory procedures, the effect of a history of subfertility was studied by comparison of the cohort to a reference group of children born to fertile couples (n=101). The fluency score, NOS and the prevalence of MND were similar in COH-IVF, MNC-IVF and NC children. However, the fluency score and NOS of the three subfertile groups were higher and the prevalence of MND was lower compared to the reference group. In conclusion, neurological condition of two-year-olds born after ART is similar to that of children of subfertile couples conceived naturally. Moreover, subfertility does not seem to be associated with a worse neurological outcome at the age of two years.

In **Chapter 6**, we studied the mental, psychomotor and behavioural development of the Groningen ART-cohort children with the Bayley Scales of Infant Development and Achenbach's Child Behaviour Checklist (CBCL). Again, the effect of a history of subfertility was studied by comparison to the reference group of children born to fertile couples. Cognitive, psychomotor and behavioural outcome in COH-IVF, MNC-IVF and NC groups was similar. Developmental outcome and behaviour of the subfertile groups was largely similar to that of the fertile reference group. Nevertheless, the subfertile groups scored higher on the scale of anxious-depressed behaviour than the reference group. In conclusion, the study suggests that cognitive and psychomotor development and behaviour at 2 years are not affected by ovarian hyperstimulation, the in vitro procedure or a history of subfertility.

Altogether the results of the studies of the Groningen ART-cohort are reassuring. It should be kept in mind that subtle neurodevelopmental disorders may emerge when children grow older. Continuation of follow-up is therefore still needed.

Part III; Follow-up of children born after IVF with Preimplantation Genetic Screening

This part evaluates the effect of preimplantation genetic screening (PGS) on neurodevelopmental outcome in children.

In **chapter 7**, we conducted a prospective follow-up study of children born to women randomly assigned to in-vitro fertilisation with or without PGS. Primary outcome was adverse neurological outcome at 18 months; secondary outcome were types of minor neurological dysfunction, neurological outcome before 18 months, neonatal intensive-care admission, and congenital malformations. Twenty women in the PGS-group participated with 25 children and 26 women in the control group participated with 31 children. Five PGS-pregnancies (25%) and 4 control-pregnancies (15%) resulted in birth of at least one child with an adverse neurological outcome. Dysfunction in fine-motor abilities and posture-and-muscle-tone dysregulation tended to be present more frequently following PGS. Neurological outcome before 18 months, neonatal intensive-care admission and prevalence of congenital malformations were similar in study and control pregnancies. Nevertheless, at child level, rates of adverse outcome were higher following PGS. In conclusion, outcome in pregnancies following IVF with and without PGS was similar. The small sample size precludes the conclusion that PGS is not associated with less favourable neurological outcome.

Chapter 8 describes the results of a follow-up study of children born to women randomly assigned to IVF with or without PGS. Mental, psychomotor,

neurological and behavioural outcome in two-year-old children was measured with the Bayley Scales of Infant Development, the Hempel neurological examination, and the Child Behaviour Check List. Participants were 54 PGS-children and 77 controls. Mental, psychomotor, and behavioural outcome at 2 years in children born following IVF with and without PGS was overall similar. Children born after PGS showed lower neurological optimality scores than control children. Scores on all tests were within the normal range. In conclusion, PGS-conception does not seem to be associated with decreased mental, psychomotor, and behavioural outcome at age 2. The lower neurological optimality scores found in children born after PGS may signal less favourable long-term neurological outcome after application of PGS.

The findings in the follow-up studies of children born after PGS stress the need of evaluation of safety of new assisted reproductive techniques before large-scale implementation.

Part IV: General discussion and future perspectives

In **Chapter 9** the findings of the studies are discussed. The results of the Groningen ART cohort study suggest no effect of ovarian hyperstimulation or the IVF procedure itself on neurodevelopmental outcome until the age of 2 years. Furthermore, follow-up of children born after ART with PGS showed no association between PGS conception and decreased mental, psychomotor, and behavioural outcome at age two, however an association was found between PGS conception and lower neurological optimality scores.

Strengths of the Groningen ART cohort study are the unique study groups, the high follow-up rate, the representative participants and the detailed, standardised, longitudinal assessments. Limitations are the relatively small sample sizes and the relatively young age at follow-up. The PGS-study's strengths are the randomisation of subfertile couples, and high participation rates. The main weakness is the relatively small sample size.

Subfertility is associated with adverse perinatal outcome. The relation between subfertility and neurodevelopmental outcome was - just as in other reports - inconsistent in our studies, possibly due to selection bias. Elucidation of the effects of subfertility would be helpful to customise obstetrical and child-welfare-care.

Future research should focus on neurodevelopmental outcome of older children, adolescents and twins. Furthermore cardiovascular outcome of ART-children deserves attention. The safety of new assisted reproductive technologies should be evaluated before large-scale implementation.