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## ARTICLE

# Subfertility factors rather than assisted conception factors affect cognitive and behavioural development of 4-year-old singletons

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**Abstract** Research on cognitive and behavioural development of children born after assisted conception is inconsistent. This prospective study aimed to explore underlying causal relationships between ovarian stimulation, in-vitro procedures, subfertility components and child cognition and behaviour. Participants were singletons born to subfertile couples after ovarian stimulation IVF ( $n = 63$ ), modified natural cycle IVF ( $n = 53$ ), natural conception ( $n = 79$ ) and singletons born to fertile couples (reference group) ( $n = 98$ ). At 4 years, cognition (Kaufmann-ABC-II; total IQ) and behaviour (Child Behavior Checklist; total problem T-score) were assessed. Causal inference search algorithms and structural equation modelling was applied to unravel causal mechanisms. Most children had typical cognitive and behavioural scores. No underlying causal effect was found between ovarian stimulation and the in-vitro procedure and outcome. Direct negative causal effects were found between severity of subfertility (time to pregnancy) and cognition and presence of subfertility and behaviour. Maternal age and maternal education acted as confounders. The study concludes that no causal effects were found between ovarian stimulation or in-vitro procedures and cognition and behaviour in children

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aged 4 years born to subfertile couples. Subfertility, especially severe subfertility, however, was associated with worse cognition and behaviour. 

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**KEYWORDS:** assisted reproduction techniques, causal inference search algorithm, cognitive and behavioural outcome, ovarian stimulation, subfertility

## Introduction

Up to 5% of European newborns are born after assisted reproduction techniques (Kupka et al., 2016). Consequently, their development and health is of general significance. Assisted reproduction techniques are associated with perinatal adversities (Pandey et al., 2012; Sutcliffe and Ludwig, 2007). These perinatal adversities, in turn, are associated with neurodevelopmental disorders, such as attention deficit hyperactive disorder and learning disabilities (Bhutta et al., 2002; De Jong et al., 2012b; Murray et al., 2016). Yet, it seems that assisted reproduction techniques are not associated with adverse cognitive and behavioural development during the first postnatal years (Middelburg et al., 2008; Yeung et al., 2016). Although reassuring, it does not preclude an association with impaired development at later age. Although only subtle signs or even no symptoms are present at early childhood, children may still grow into neurodevelopmental deficits at older age, as it may take time for developmental disorders to emerge (Hadders-Algra, 2002). In addition, over time, genetic effects on intelligence and behaviour may get increasingly expressed owing to the long-lasting interaction with social conditions (Bates et al., 2013; Brendgen et al., 2015).

Various factors related to assisted reproduction techniques could potentially interfere with development, such as ovarian stimulation (Griesinger et al., 2008), in-vitro procedures (Olivennes et al., 1993), the effect of underlying subfertility on time to pregnancy (TTP), (Basso and Baird, 2003; Draper et al., 1999; Jaques et al., 2010; Raatikainen et al., 2012) and the effect of parental characteristics on educational level (Jolly et al., 2000; Salem Yaniv et al., 2010; Tornqvist et al., 2010).

Results of long-term studies on cognitive and behavioural development in children born via assisted reproduction techniques vary, partly owing to difficulties in distinguishing relationships between assisted reproduction techniques and underlying characteristics of subfertility, parents and child. Other factors that may explain the diversity in study outcomes may be the age at which children were studied (varying from 5–26 years), total sample sizes (varying from 69–45,557 children), sex ratios (the proportion of females varying from 37.5–52%) and the instruments used to assess outcome (among others the Teacher's Report Form, Stanford-Binet Intelligence Scale, Revised Amsterdam Child Intelligence Test, Iowa Tests of Basic Skills/Educational Development, Wechsler Intelligence Scale for Children-Revised). As a consequence, cognitive and behavioural outcome of children born via assisted reproduction techniques has been reported as similar (Leslie et al., 2003; Leunens et al., 2008; Ludwig et al., 2009; Wagenaar et al., 2009b; Zhu et al., 2011), worse (Knoester et al., 2007, 2008; Goldbeck et al., 2009; Wagenaar et al., 2009a; Zhu et al., 2009; Beydoun et al., 2010; Gucuyener

et al., 2011) or better (Leunens et al., 2006; Mains et al., 2010) than that of naturally conceived children.

To investigate the influence of specific factors involving assisted conception on developmental outcome, we composed the Groningen assisted reproduction technique cohort. It consists of three groups of singletons born to subfertile couples: children born after conventional ovarian stimulation with IVF and intracytoplasmic sperm injection (ICSI), children born after modified natural cycle IVF-ICSI (MNC-IVF), and children born after natural conception (Sub-NC) (Middelburg et al., 2010). We previously reported on neurodevelopmental and cardiometabolic outcome of the Groningen assisted reproduction technique cohort until 4 years of age. Developmental outcome of the groups was similar up to the age of 2 years (Middelburg et al., 2009, 2010; Schendelaar et al., 2011, 2013). A negative association was found between the duration of subfertility (TTP) and neurological condition at 2 and 4 years, suggesting that the severity of subfertility rather than its presence or the assisted reproduction technique components affect neurological outcome (Schendelaar et al., 2014; Seggers et al., 2013). Cognitive and behavioural development within the Groningen assisted reproduction technique cohort was studied up to the age of 2 years. We reported no differences in cognitive and behavioural outcome between the three study groups. Children of the three subfertile study groups, however, had higher scores on anxious and depressed behaviour than the children from a reference group born to fertile parents (Jongbloed-Pereboom et al., 2011).

In a previous study at 4 years, we applied a causal inference approach to evaluate factors affecting anthropometrics and cardiovascular health. The study indicated direct positive effects of children born after OS-IVF and not of children born after MNC-IVF on outcomes, suggesting that ovarian stimulation was involved in worse cardiometabolic health (La Bastide-Van Gemert et al., 2014; Seggers et al., 2014).

Unlike traditional statistics, a causal inference approach is able to unravel underlying causal mechanisms and distinguish between confounders and intermediate effects. This makes it an appropriate tool to explore relationships between assisted reproduction techniques and underlying characteristics of subfertility, parents and child. The primary aim of this study is to explore underlying causal relationships between ovarian stimulation, the in-vitro procedure and the combination of both and cognition and behaviour in 4-year-old singletons. Second, we aim to explore the underlying causal relationships between two aspects of subfertility and cognition and behaviour. We addressed the contribution of the presence of a history of subfertility by including a reference group of 4-year-old singletons born to fertile parents, and the duration of subfertility in terms of TTP, as a proxy for the severity of subfertility. We have chosen cognitive outcome as our primary outcome parameter, as cognition has a stronger

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