Human Reproduction, Vol.31, No.1 pp. 100–107, 2016
Advanced Access publication on October 29, 2015 doi:10.1093/humrep/dev273

human reproduction

ORIGINAL ARTICLE *Infertility*

Mental health and developmental outcomes for children born after ART: a comparative prospective study on child gender and treatment type

Raija-Leena Punamäki[1,*], Aila Tiitinen[2,3], Jallu Lindblom[1], Leila Unkila-Kallio[2,3], Marjo Flykt[1], Mervi Vänskä[1], Piia Poikkeus[2,3], and Maija Tulppala[2]

[1]School of Social Sciences and Humanities, Department of Psychology, University of Tampere, Tampere, Finland [2]Department of Obstetrics and Gynaecology, Helsinki University Central Hospital, Helsinki, Finland [3]University of Helsinki, Helsinki, Finland

*Correspondence address. University of Tampere, School of Social Sciences and Humanities/Psychology, FIM-33014 University of Tampere, Kalevankatu 5, Linna 4krs, Finland. Tel: +358-50-3186187; Fax: +358-3-341-900-06; E-mail: raija-leena.punamaki@uta.fi

Submitted on March 26, 2015; resubmitted on September 15, 2015; accepted on October 8, 2015

STUDY QUESTION: Do children born after assisted reproductive techniques (ART; IVF/ICSI) display more mental health issues or social and cognitive developmental problems at 7–8 years than naturally conceived (NC) controls, and does child gender play a role?

SUMMARY ANSWER: ART children do not differ with regard to mental health or social and cognitive developmental problems when compared with controls, but some gender-specific differences do exist.

WHAT IS KNOWN ALREADY: Systematic reviews have not found any evidence of delays in neurocognitive or sensorimotor development in ART children. However findings on the effect of the type of ART treatment (IVF versus ICSI) on the offspring's physical and mental development have not been uniform. Knowledge of the role of child gender in ART research is scarce.

STUDY DESIGN, SIZE, DURATION: This prospective follow-up study compares mental health and social and cognitive developmental problems between 7–8-year-old ART and NC children, controlling for the father's age, length of the parents' partnership, mother's parity, child's gestational age, and the need of neonatal intensive care unit (NICU). Further, within the ART group, we analysed whether the treatment type (IVF versus ICSI) and the child's gender are associated with the mental health and developmental outcomes.

PARTICIPANTS/MATERIALS, SETTING, METHODS: In this study, 255 singleton ART children (IVF and ICSI) were compared with 278 NC children on parent-reported internalizing and externalizing symptoms, and social (social skills and peer relations) and cognitive development (executive functioning, perception, memory, and language). Within the ART group, 164 IVF and 76 ICSI children were compared on the same outcomes. Statistics included analyses of covariates (ANCOVA) with group main effects, group and gender interaction effects, and Bonferroni *post hoc* tests.

MAIN RESULTS AND THE ROLE OF CHANCE: ART and NC children did not differ generally in terms of their internalizing and externalizing symptoms or in the number of social and cognitive developmental problems (Group main effects, $P > 0.05$), but gender-specific group differences existed. The ART boys showed lower levels of cognitive problems than the NC boys, whereas ART girls showed higher levels of cognitive problems than the NC girls (Group × Gender-interaction effects with Bonferroni *post hoc* tests on mother-reports, $P < 0.01$). Further, unlike in the NC group, where boys showed more externalizing symptoms and social and cognitive developmental problems than girls (Group × Gender-interaction effects with Bonferroni *post hoc* tests for both parents' reports, $P < 0.05$), gender differences were not found in the ART group. Within the ART group, IVF and ICSI children did not differ in terms of mental health or developmental outcomes, and no significant gender differences emerged.

LIMITATIONS, REASONS FOR CAUTION: The information on children's mental health and development was based on parental reports only. The dropout rate between the child's first year and the school age assessments was very high for fathers (57.4%) and substantial for mothers (30.1%), and the participating group was biased for older age of both parents and for better education of the fathers.

WIDER IMPLICATIONS OF THE FINDINGS: The findings indicate the importance of considering child gender in learning about multiple developmental outcomes among children born after ART.

STUDY FUNDING/COMPETING INTEREST(S): This study was supported by the Academy of Finland (#11232276), the Emil Aaltonen Foundation, The Family Federation of Finland, Helsinki University Central Hospital Research Funds, and the National Graduate School of Psychology. None of authors has any competing interests to declare.

Key words: ART / IVF / ICSI / cognitive development / social development / mental health / school-age children

Introduction

Concerns exist about the physical health, growth and neurocognitive development of children born as a result of assisted reproduction techniques (ART), including *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI). Some early neurocognitive and sensorimotor developmental delays and deficits have occasionally been reported among ART children, but those are partially explained by the increased perinatal problems (e.g. preterm birth, low birthweight and admission to neonatal intensive care) inherent in ART pregnancies.

Generally, no developmental differences are found between ART and naturally conceived (NC) children, if perinatal and obstetric problems are controlled (for reviews see Pandey *et al.*, 2012; Hansen *et al.*, 2013; Abdel-Mannan *et al.*, 2014). A multi-country study ($n = 566$) comparing ICSI and NC children found similar intellectual performances (IQ) among 5-year-olds (Ponjaert-Kristoffersen *et al.*, 2004), and a follow-up study at the age of 8–10 years confirmed the result concerning overall, verbal, and performance IQs (Leunens *et al.*, 2006, 2008). Additionally a multi-site five-country study ($n = 1423$) showed no differences between IVF, ICSI, and NC adolescents in cognitive information processing, attention, or visual-motor functioning (Wagenaar *et al.*, 2008).

Concerning mental health and socio-emotional development, the outcomes of ART children have been comparable to or even better than those of NC children (Wagenaar *et al.*, 2009, 2011; Hart and Norman, 2013). When studying 5-year-olds, two multi-country European studies reported no differences in mental health or socio-emotional well-being between IVF and NC (Barnes *et al.*, 2004) or between ICSI and NC children (Ponjaert-Kristoffersen *et al.*, 2004). Similarly, a study matching ICSI/IVF and NC children reported no differences in conduct or emotional problems among 5–8-year-olds (Knoester *et al.*, 2007). Evidence of better mental health among ART children comes from studies showing fewer parent-reported conduct and emotional problems among ICSI toddlers compared with NC toddlers (Nekkebroeck *et al.*, 2008), and fewer parent- and teacher-reported externalizing symptoms (e.g. aggression and rule-breaking behaviour) among IVF 9–18-year-olds compared with NC 9–18-year-olds (Wagenaar *et al.*, 2009). When these children themselves were informants in a 2-year follow-up, no differences were found neither in externalizing nor internalizing symptoms (e.g. depression and anxiety) (Wagenaar *et al.*, 2011).

Gender differences are generally obvious and well-documented in infant and child development (Karama *et al.*, 2011; Skeer *et al.*, 2011), but only seldom considered in ART studies. One study found no differences between IVF and NC girls and boys in internalizing or externalizing problems (Cederblad *et al.*, 1996), while another reported that IVF girls had lower levels of mental health problems than NC or ICSI girls (Knoester *et al.*, 2007). A third, large cohort study ($n = 1525$), found a lower occurrence of left-handedness in ICSI than in NC girls, while the mode of conception made no difference in boys (Sutcliffe *et al.*, 2008). In general, girls are more vulnerable to depression and anxiety and boys are more vulnerable to aggressive and antisocial symptoms (Weller *et al.*, 2006; Skeer *et al.*, 2011). With regard to cognitive development, girls usually score higher in verbal intelligence (e.g. language) and boys score higher in performance (e.g. visuospatial perception) (Karama *et al.*, 2011).

The present study examined, first, whether mental health and social and cognitive development differ between ART and NC children at the age of 7–8 years. Second, within the ART group, we examined the role of treatment type (IVF or ICSI) in predicting children's mental health and social and cognitive development. Third, the role of child's gender was analysed as a possible moderator in the associations.

Materials and Methods

Participants and study procedure

Couples who conceived by ART in Finnish fertility clinics and NC control couples undergoing a routine ultrasound examination were recruited for a prospective study in 1999. They participated at 18–20 weeks of gestation (T1; $n = 860$), and 2 months (T2; $n = 711$) and 12 months (T3; $n = 587$) post-partum. The families participated again when the children were 7–8 years old (T4; $n = 533$). The questionnaires were sent home and the participants returned them in pre-paid envelopes to the research nurse (T1–T3) and researchers (T4). The Ethical Committees in the participating clinics approved the study at each assessment time.

The present study included couples with singleton pregnancies from their own gametes. At T4, 255 ART families and 278 NC families participated, with mothers participating more actively ($N = 520$; 69.9% from T1 singletons) than fathers ($N = 303$; 42.6%). In 13 cases, only the father responded. In the ART group, there were 164 (68.3%) IVF-conceived and 76 (31.7%) ICSI-conceived children, while this information was not provided for 15 children. The mean age of the children was 7.4 $\pm$ 0.6 years, and 49% ($n = 259$) were girls and 51% ($n = 274$) boys.

Attrition analysis revealed that the parents who participated in T4 were older than the dropout parents (mothers 41.3 $\pm$ 3.8 versus 40.7 $\pm$ 3.6 years, $t = 3.01$, $P < 0.01$; fathers 44.2 $\pm$ 5.0 versus 42.7 $\pm$ 5.6 years, $t = 2.6$, $P < 0.05$). The participating fathers were better educated than dropout fathers ($\chi^2(4) = 4.10$, $P < 0.01$). The attrition at T4 for both mothers and fathers was independent of the length of the marriage, the number of children, the number of earlier partnerships, and their mental health measured at T1–T3. Moreover, the child's gender, birthweight, and gestational age at birth did not differ between the participating and non-participating couples. Finally, both maternal and paternal participation at T4 was independent of the ART treatment type (IVF or ICSI).

Measures

Obstetric, treatment and demographic information was collected from the records of infertility and maternity clinics by the recruiting doctors or by

the research nurse at T1, and from mothers at T2. Both parents reported their age, marital status, number of previous marriages, parity, and socio-economic status (SES) at T1.

The *child's mental health problems* were measured by the Parent Rating Scales (PRS-C) of the Behavioral Assessment System for Children (BASC) (Reynolds and Kamphaus, 1992). The scale comprised 50 symptoms covering four domains: Anxiety (12 items), Depression (12 items), Somatization (13 items), and Aggression (13). Mothers and fathers separately rated the child's symptoms on a 4-point scale, ranging from 1 = never to 4 = almost always. An *internalizing symptoms scale* was constructed, comprising averaged anxiety, depression, and somatization symptoms separately on both parents' responses (Cronbach's α reliabilities 0.69 for mothers; 0.79 for fathers). The *externalizing symptoms scale* included only the averaged aggression symptom sums ($\alpha = 0.83$ for mothers; $\alpha = 0.85$ for fathers).

The *child's social developmental problems* were measured by the 10-item Assertion-dimension of the parent version of the Social Skills Rating System (SSRS) (Gresham and Elliot, 1990) and by the 7-item Excluded by Peers-dimension of Child Behaviour Scale (CBS) (Rutter, 1967). Both parents separately rated the child's behaviour on a 4-point scale, ranging from 1 = never to 4 = very often. Averaged sum variables were calculated by combining the Assertion- and Excluded by peers-dimensions, indicating social developmental problems, separately for mothers' and fathers' responses ($\alpha = 0.78$ for mothers; $\alpha = 0.79$ for fathers).

The *child's cognitive developmental problems* were assessed by the parental questionnaire Five to Fifteen (FTF) which is a developmental screening instrument for early childhood onset of neuropsychiatric disorders such as ADHD (Kadesjö *et al.*, 2004). Of the eight domains of the original FTF, four most salient domains for this age group were chosen: *executive functions* (e.g. planning and organizing), *perception* (e.g. time concepts and visual perception), *memory* (e.g. semantic memory and episodic memory) and *language functioning* (e.g. communication skills). Both parents separately rated the child's capacity on a 3-point scale, ranging from 0 = does not apply to 2 = definitely applies. Averaged sum variables combining all cognitive problems were calculated separately on mothers' and fathers' responses ($\alpha = 0.75$ for mothers; $\alpha = 0.84$ for fathers).

Statistical analyses

To analyse the group and gender differences in child's mental health and development, we conducted 2 (Group: ART versus NC) × 2 (Gender) ANCOVAs with main and interaction effects on internalizing and externalizing symptoms, and social and cognitive developmental problems. In case the interaction effects were statistically significant, the differences between subgroups (i.e. ART girls versus NC girls or ART boys versus NC boys, or between boys and girls within ART and NC) were further checked by Bonferroni *post hoc* tests. The covariates were father's age, length of partnership, mother's parity, child's gestational age at birth, and need of NICU, because the ART and NC groups differed in terms of these aspects.

To test the impacts of the treatment type, we conducted 2 (IVF versus ICSI) × 2 (Gender) ANCOVAs with main and interaction effects, on internalizing and externalizing symptoms, and social and cognitive developmental problems, with Bonferroni *post hoc* tests. The number of ART treatments was used as a covariant as the IVF and ICSI groups differed in this aspect. The statistical significance level was $P < 0.05$. The Statistical Package for Social Science (SPSS) Windows version 22.0 was used for all analyses.

Results

Descriptive statistics

Table I presents the demographic, obstetric, and perinatal characteristics in the ART and NC groups, and within ART between the IVF and ICSI groups. ART children differed from NC children in three aspects: they were more often firstborn (women were primiparous) and preterm, and had need of NICU. The ART fathers were older ($M = 43.27 \pm 5.74$) than the NC fathers ($M = 42.14 \pm 5.74$), $t(462) = 2.11$, $P < 0.03$, while the groups did not differ in maternal age (ART mothers $M = 41.42 \pm 4.30$; NC mothers $M = 41.33 \pm 3.01$, $t(531) = 0.49$, $P =$ ns). The ART couples also had longer partnerships ($M = 114 \pm 54$ months) than the NCs ($M = 93 \pm 51$ months), $t(531) = 4.60$, $P < 0.001$. The average number of children was lower in the ART ($M = 1.50 \pm 0.64$) than in the NC ($M = 1.86 \pm 0.92$) families, $t(531) = -5.03$, $P < 0.0001$, at T4.

The only significant difference between IVF and ICSI groups was the higher total number of unsuccessful treatments in the IVF ($M = 3.8 \pm 2.3$) than in the ICSI (2.8 ± 2.0) group, $t(221) = 3.27$, $P < 0.001$.

Mental health among ART and NC children

Table II presents means and standard errors of mother-reported and Table III father-reported data on mental health among the ART and NC children according to gender. The results show that ART and NC children did not generally differ in their internalizing and externalizing symptoms reported by either parent. However, the Group × Gender-interaction effects were significant on externalizing symptoms (Mother-reported: $F(1,509) = 8.62$, $P < 0.003$, partial $\eta^2 = 0.02$; Father-reported; $F(1,302) = 4.49$, $P < 0.05$, partial $\eta^2 = 0.01$), indicating that gender had a different role in ART and NC children's symptoms. The NC boys showed more externalizing symptoms than the NC girls (Bonferroni *post hoc* tests $P < 0.009$ for mothers' and $P < 0.007$ for fathers' reports), while no differences were found between boys and girls in the ART group. Parity was a significant covariant for mother-reported internalizing ($F(1,509) = 10.09$, $P < 0.002$, partial $\eta^2 = 0.02$) and externalizing ($F(1,509) = 11.82$, $P < 0.001$, partial $\eta^2 = 0.02$) symptoms. Women with more children reported lower levels of these symptoms.

Social and cognitive developmental problems among ART and NC children

Means and standard errors of social and cognitive developmental problems reported by mothers are in the lower part of Table II and by fathers in Table III. Both results show that ART and NC children did not generally differ in their social or cognitive developmental problems. Instead, the Group × Gender-interaction effects were significant on social (Mother-reported: $F(1,509) = 4.70$, $P < 0.03$, partial $\eta^2 = 0.01$; Father-reported: $F(1,302) = 4.13$, $P < 0.04$, partial $\eta^2 = 0.01$) and cognitive (Mother-reported: $F(1,509) = 19.72$, $P < 0.0001$, partial $\eta^2 = 0.04$; Father-reported: $F(1,302) = 11.72$, $P < 0.001$, partial $\eta^2 = 0.04$) developmental problems.

Concerning social developmental problems, Bonferroni *post hoc* tests were significant only for mothers' reports, showing that in the NC group boys showed more social developmental problems than girls ($P < 0.03$), while in the ART no gender differences were found. Of the covariates, fathers' age was significant in the father-reported model for social developmental problems ($F(1,302) = 4.40$, $P < 0.04$, partial $\eta^2 = 0.02$), with the younger fathers reporting a higher level of problems.

Concerning cognitive developmental problems, ART boys showed lower levels of these problems than NC boys (Bonferroni *post hoc* test, $P < 0.008$), whereas ART girls had more cognitive problems than NC girls ($P < 0.02$) according to mothers' reports only. Furthermore, in the NC group, boys had more cognitive developmental problems than

Table I Descriptive characteristics of the participants and obstetric and perinatal outcomes of the pregnancy in the ART versus NC groups ($n = 533$) and in the IVF versus ICSI groups ($n = 240$).

	ART group $N = 255$ % (n)	NC group $N = 278$ % (n)	χ^2 values	IVF group $N = 164$ % (n)	ICSI group $N = 76$ % (n)	χ^2 values
Family SES			2.66			1.20
High professional	35.7 (91)	39.9 (111)		39.0 (64)	35.6 (27)	
Low professional	46.7 (119)	43.5 (121)		43.8 (72)	43.4 (33)	
Skilled worker	14.5 (37)	15.1 (42)		13.5 (22)	18.4 (14)	
Unskilled worker	3.1 (8)	1.4 (4)		3.7 (6)	2.6 (2)	
Parity			52.74***			0.60
Primiparous	67.5 (172)	36.0 (100)		70.5 (103)	67.1 (49)	
Multiparous	32.5 (83)	64.0 (178)		29.5 (43)	32.9 (24)	
Marital status			4.52			1.51
Married	76.9 (196)	68.7 (191)		73.8 (121)	80.3 (61)	
Cohabitant	22.7 (58)	30.9 (86)		25.6 (42)	19.7 (15)	
Divorced	0.4 (1)	0.4 (1)		0.6 (1)	0.0 (0)	
Previous partnerships			1.15			1.37
None	69.8 (178)	65.5 (182)		68.4 (104)	76.1 (54)	
One	24.7 (63)	28.1 (78)		26.3 (40)	19.7 (14)	
Two or more	5.5 (14)	6.5 (18)		5.3 (8)	4.2 (3)	
Child's gender			1.12			0.58
Boy	49.0 (125)	53.6 (149)		51.2 (84)	47.4 (36)	
Girl	51.0 (130)	46.4 (129)		48.8 (80)	52.6 (40)	
Child birthweight (g)			3.56			2.18
>2500	96.1 (245)	98.6 (274)		96.3 (158)	94.7 (72)	
1500–2499	3.5 (9)	1.4 (4)		3.7 (6)	3.9 (3)	
<1500	0.4 (1)	0.0 (0)		0.0 (0)	1.3 (1)	
Gestational age at birth			6.15*			2.28
>37 weeks	92.5 (236)	97.1 (270)		92.1 (151)	92.1 (70)	
32–36 weeks	7.1 (18)	2.9 (8)		7.9 (13)	6.6 (5)	
<32 weeks	0.4 (1)	0.0 (0)		0.0 (0)	1.3 (1)	
Need of NICU			8.31*			0.67
No	80.0 (204)	87.8 (244)		78.7 (129)	81.6 (62)	
Follow-up ward	15.7 (40)	11.2 (31)		17.1 (28)	13.2 (10)	
NICU[a]	4.3 (11)	1.1 (3)		4.3 (7)	5.3 (4)	

[a]NICU, neonatal intensive care unit.
*$P < 0.05$, ***$P < 0.001$.

girls (Bonferroni *post hoc* tests $P < 0.0001$ for both mother-reported and father-reported data), while no gender differences related to cognitive developmental problems existed in the ART group. Figure 1 presents the cognitive developmental problems among ART and NC children according to their gender, as reported by mothers. None of the covariates were significant for mother- or father-reported cognitive developmental problems.

Type of ART treatment and children's mental health and development

In general, no significant differences were found in mental health or social and cognitive development problems between children born after IVF versus ICSI (ANCOVA data not shown). A significant Treatment type × Gender-interaction effect ANCOVA was found for father-reported social development ($F(1,160) = 9.40$, $P < 0.003$, partial $\eta^2 = 0.06$), but the Bonferroni *post hoc* test indicated non-significant gender effects.

Discussion

This study compared mental health and developmental outcomes between ART and NC children, and the results confirmed the earlier view that ART is not generally associated with increased problems in child mental health or cognitive and social development (Bay *et al.*,

Table II Mother-reported data. Means, standard errors and ANCOVA-statistics in ART and naturally conceived (NC) groups[1] according to child gender[2] on mental health problems, and social and cognitive developmental problems ($n = 510$).

		ART children		NC children		ANCOVA *F*-values		
		M	SE	*M*	SE	Group main effect	Gender main effect	Group × Gender interaction effect
Mental health problems [3,4,5]								
Internalizing	Girls	1.49	0.02	1.43	0.02	0.41	0.22	1.66
	Boys	1.45	0.02	1.46	0.02			
Externalizing	Girls	1.63[a]	0.03	1.57[ab]	0.03	2.06	13.26****	8.62**
	Boys	1.65[a]	0.03	1.70[ac]	0.03			
Social problems[3,4,5]	Girls	2.67[a]	0.03	2.65[ab]	0.03	0.02	1.77	4.70*
	Boys	2.68[a]	0.03	2.76[ac]	0.02			
Cognitive problems[3,4,5]	Girls	1.30[a]	0.02	1.22[b]	0.02	0.13	12.14***	19.72****
	Boys	1.28[ab]	0.02	1.38[c]	0.02			

Note: [1]ART (IVF/ICSI), $n = 249$ and NC, $n = 261$; [2]ART girls, $n = 125$ and ART boys, $n = 124$, NC girls, $n = 120$ and SC boys, $n = 141$; [3]Group and gender main effects and Group × Gender-interaction effects when father's age, length of the partnership, mother's parity, gestational age at birth, and need of NICU are the covariates; [4]In the scales of internalizing and externalizing symptoms, and social and cognitive problems high values indicate problematic development; [5]Bonferroni *post hoc* test (< 0.05) results are indicated by different upper letters between ART and NC boys and girls.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$.

Table III Father-reported data. Means, standard errors and ANCOVA-statistics in ART and naturally conceived (NC) groups[1] according to child gender[2] on mental health problems, and social and cognitive developmental problems ($n = 303$).

		ART children		NC children		ANCOVA *F*-values		
		M	SE	*M*	SE	Group main effect	Gender main effect	Group × Gender interaction effect
Mental health problems[3,4,5]								
Internalizing	Girls	1.45	0.03	1.43	0.03	0.30	0.73	2.31
	Boys	1.43	0.03	1.49	0.03			
Externalizing	Girls	1.63[a]	0.04	1.55[ab]	0.04	0.02	11.07***	4.49*
	Boys	1.60[a]	0.04	1.73[ac]	0.04			
Social problems[3,4,5]	Girls	2.66	0.03	2.65	0.03	0.03	0.73	4.13*
	Boys	2.69	0.03	2.74	0.02			
Cognitive problems[3,4,5]	Girls	1.29[a]	0.03	1.20[ab]	0.02	0.15	8.44***	11.72***
	Boys	1.28[a]	0.03	1.37[ac]	0.03			

Note: [1]ART (IVF/ICSI), $n = 169$ and NC, $n = 134$; [2]ART girls, $n = 81$ and ART boys, $n = 88$, NC girls, $n = 67$ and NC boys, $n = 67$; [3]Group and gender main effects and Group × Gender-interaction effects when father's age, length of the partnership, mother's parity, gestational age at birth, and Need of NICU are the covariates; [4]In mental health and social and cognitive scales high values indicate problematic development; [5]Bonferroni *post hoc* test (< 0.05) results are indicated by different upper letters between ART and NC boys and girls.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

2013; Hart and Norman, 2013). Former research has seldom considered the role of gender in comparing ART and NC children, but our results suggest two gender-specific phenomena. First, ART boys showed less cognitive developmental problems than NC boys, whereas ART girls' cognitive problems exceeded those of NC girls', but only when the maternal report was used. Second, normative gender differences in higher aggression and social and cognitive developmental problems among boys were present only in the NC group, whereas ART boys and girls did not differ from each other.

Our findings add to the evidence of comparable mental health and social and cognitive development in ART children, when peri- and postnatal risk factors are controlled. However, in our study ART boys performed better than NC boys, and ART girls performed worse than NC girls in cognitive domains, indicated by executive functioning, perception, memory, and language development. It is noteworthy that within the ART group, boys and girls had similar performances.

Prenatal factors and infertility-related family dynamics may explain the relatively better cognitive development among ART boys as compared with NC boys. Research suggests that the quality of the fetal development and programming particularly predicts cognitive performance (Davis and Sandman, 2010; Buss *et al.*, 2011). Male fetuses are more vulnerable than females to maternal stress and other prenatal medical and

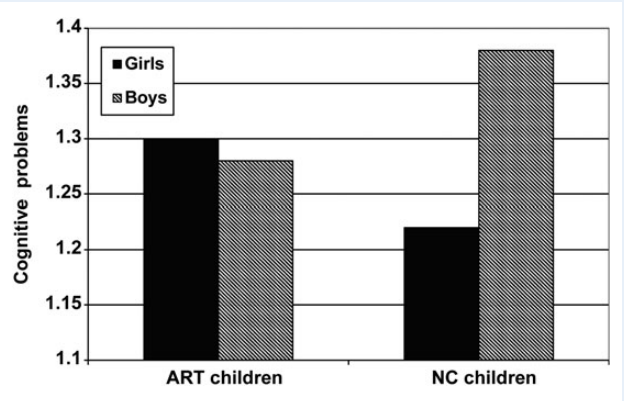

Figure 1 Cognitive developmental problems reported by mothers among ART (IVF/ICSI, $n = 249$) and naturally conceived (NC, $n = 261$) girls and boys. The numbers on the *Y*-axis refer to mean values for cognitive problems.

behavioural risks (Vatten and Skjaerven, 2004; Risnes *et al.*, 2009), leading to lower proportion of male births (Rueness *et al.*, 2012). One may speculate that the better cognitive performance of ART boys may partially be due to the fetal selection process.

Parents with a history of infertility perceive their children as more precious and special due to their high material and emotional investment in becoming pregnant (Gibson *et al.*, 2000; Barnes *et al.*, 2004). This may partly explain the findings of ART children showing similar or even better developmental outcomes or performing well despite their early obstetric risk factors. Yet, our results specify that the beneficial resources were valid particularly for boys concerning cognitive developmental problems in middle childhood.

The active participation of fathers in child rearing is characteristic of ART families, attributed to the high motivation and commitment needed in ART treatments (Hjelmstedt and Collins, 2008; Bracks-Zalloua *et al.*, 2011). A warm and supportive father-child relationship is considered important for the child's mental health and cognitive development (Ramchandani *et al.*, 2008; Volker, 2014), and some argue that optimal fathering is particularly crucial in the development of boys, at least in middle childhood (Stroud *et al.*, 2011). Encouragement and positive attitudes toward the 'precious child', combined with the fathers' high commitment, possibly contributes to the boys' superior cognitive development in ART families.

It is worthwhile considering why girls did not appear to benefit from the greater parental commitment and favourable rearing ethos of ART families. Developmental research emphasizes that children respond differently to the same family environment, depending on, for example, their temperament, order in siblingship, and gender (Plomin *et al.*, 2001). Being a 'precious' child in an ART family can also signify excessive expectations directed toward the child. It is possible that girls are more sensitive to parental pressure to achieve, and the resulting stress could interfere with their cognitive performance. However, the view is speculative as we have not analysed possible gender-specific parenting practices, family interactions, or expectations in ART and NC families. Some studies show similar or better-than-average parenting practices in ART families, indicated, for example, by lower parental stress (Repokari *et al.*, 2006) and comparable intimacy and autonomy in family relationships (Flykt *et al.*, 2014; Lindblom *et al.*, 2014). Other studies instead have revealed higher parenting stress and concern for children among ICSI than NC parents (Knoester *et al.*, 2007), and a multi-site comparative study found a large number of parenting problems in ART families in some countries (Nekkebroeck *et al.*, 2009).

Boys and girls differ greatly in their mental health and development, and normative gender differences emerge, particularly in preadolescence (e.g. Karama *et al.*, 2011; Skeer *et al.*, 2011). ART children differed from the NC controls in terms of the complete lack of gender differences in externalizing symptoms or developmental problems. The gender differences in the NC children in turn correspond with general research, as boys were more aggressive, and had more social and cognitive developmental problems than girls.

Family dynamic and child developmental characteristics may explain the lack of normative gender differences in child development in ART families. According to the 'precious child' view, parents perceive the child born following ART possibly more as a child and less as a girl or a boy, which may reflect in similar rearing opportunities for both. Further, lack of gender differences could be due to a later timing of puberty in ART as compared with NC children (Zahn-Waxler *et al.*, 2008), thus, the normative gender differences would emerge later in ART children. Unfortunately we do not have data on hormonal or other characteristics on pubertal development, which could have substantiated that hypothesis. Further research should combine roles of obstetric factors, fetus- and neonatal development, and family dynamics as possible explanations for the 'unique gender roles' in ART children.

Finally, similar to a majority of earlier studies (e.g. Barnes *et al.*, 2004; Ponjaert-Kristoffersen *et al.*, 2004), within the ART group, we did not find significant differences in mental health or cognitive or social developmental problems between IVF and ICSI children. In our clinics, ICSI is used only when male factor is present, so we could have expected distinct family dynamic characteristics. Male-related infertility has been suggested to signify low self-esteem and despair especially for men, while women may more easily find alternative ways of caring (Nekkebroeck *et al.*, 2009). Yet, the infertility background or treatment type did not reflect differently in boys' and girls' mental health or developmental problems.

Limitations of the study

Despite its prospective nature and relatively large sample size, this study has certain limitations. First, the results are based on parents' reports on their children's mental health and development, which makes them sensitive to biases. Standardized tests for cognitive development, such as the Wechsler Intelligence Scale for Children (WISC) or the Developmental NEuroPSYchological Assessment (NEPSY), would have provided more reliable assessments of children's executive functioning, perception, memory, and language capacities. However, the applied questionnaire was based on the NEPSY, and parents' responses showed high reliabilities. Similarly, the utilizing child's own as well as peer accounts, like sociograms, would have provided more reliable assessments of children's social relationships. Second, the dropout of fathers was substantial (57%), which limits the generalizability of the results of the father-reported child development. The attrition was not systematically related to demographic or obstetric characteristics, but was related to younger paternal age and lower paternal socio-economic status.

We can conclude that ART boys and girls show mental health and social performances comparable to that of NC children. Boys with an

ART background appear to enjoy additional resources, as they showed lower levels of cognitive developmental problems than other boys. On the contrary, ART girls were more vulnerable to cognitive problems compared with girls who were naturally conceived.

Acknowledgements

The authors are grateful to the families who participated in our longitudinal study. They also thank research nurse Riitta Luhtio, and all others working at the clinics, who made the data collection possible.

Authors' roles

The prospective study at T1, T2 and T3 was designed by A.T. and M.T., and the study at T4 was designed by R.-L.P. and J.L. The data was collected by L.U.-K., P.P., J.L., M.V., and M.F. R.-L.P. and L.U.-K. analysed the data, and R.-L.P., L.U.-K., and A.T. wrote originally the paper. All co-authors interpreted the data, and participated in finalizing the manuscript. All co-authors approved the final version of the manuscript.

Funding

This study was supported by research grants from the Academy of Finland (#11232276), the Emil Aaltonen Foundation, The Family Federation of Finland, Helsinki University Central Hospital Research Funds, and the National Graduate School of Psychology.

Conflict of interest

None declared.

References

Abdel-Mannan O, Basatemur E, Sutcliffe AG. I was born following ART: how will I get on at school? Review. *Semin Fetal Neonatal Med* 2014; **19**:245–249.

Barnes J, Sutcliffe AG, Kristoffersen I, Loft A, Wennerholm U, Tarlatzis BC, Kantaris X, Nekkebroeck J, Hagberg BS, Madsen SV *et al.* The influence of assisted reproduction on family functioning and children's socio-emotional development: results from a European study. *Hum Reprod* 2004;**19**:1480–1487.

Bay B, Mortensen EL, Kesmodel US. Assisted reproduction and child neurodevelopmental outcomes: a systematic review. *Fertil Steril* 2013; **100**:844–853.

Bracks-Zalloua P, McMahon C, Gibson F. IVF-conceiving fathers' experiences of early parenthood. *J Relat Res* 2011;**2**:1–9.

Buss C, Davis EP, Hobel CJ, Sandman CA. Maternal pregnancy-specific anxiety is associated with child executive function at 6–9 years age. *Stress* 2011;**14**:665–676.

Cederblad M, Friberg B, Ploman F, Sjoberg NO, Stjernqvist K, Zackrisson E. Intelligence and behaviour in children born after in-vitro fertilization treatment. *Hum Reprod* 1996;**11**:2052–2057.

Davis EP, Sandman CA. The Timing of prenatal exposure to maternal cortisol and psychosocial stress is associated with human infant cognitive development. *Child Dev* 2010;**81**:131–148.

Flykt M, Palosaari E, Lindblom J, Vänskä M, Poikkeus P, Repokari L, Tiitinen A, Tulppala M, Punamäki RL. What explains violated expectations of parent–child relationship in transition to parenthood? *J Fam Psychol* 2014; **28**:148–159.

Gibson FL, Ungerer JA, Tennant CC, Saunders DM. Parental adjustment and attitudes to parenting after in vitro fertilization. *Fertil Steril* 2000; **73**:565–574.

Gresham FM, Elliot SN. *Social Skills Rating System. Manual*. Circle Pines: American Guidance Service, 1990.

Hansen M, Kurinczuk JJ, Milne E, de Klerk N, Bower C. Assisted reproductive technology and birth defects: a systematic review and meta-analysis. *Hum Reprod Update* 2013;**19**:330–353.

Hart R, Norman RJ. The longer-term health outcomes for children born as a result of IVF treatment. Part II—Mental health and development outcomes. *Hum Reprod Update* 2013;**19**:244–250.

Hjelmstedt A, Collins A. Psychological functioning and predictors of father–infant relationship in IVF fathers and controls. *Scand J Caring Sci* 2008; **22**:72–78.

Kadesjö B, Janols L-O, Korkman M, Mickelsson K, Strand G, Tillingsgaard A, Gillberg C. The FTF (Five to Fifteen): the development of a parent questionnaire for the assessment of ADHD and comorbid conditions. *Eur Child Adolesc Psychiatry* 2004;**13**:3–13.

Karama S, Colom R, Johnson W, Deary IJ, Haier R, Waber DP, Lepage C, Ganjavi H, Jung R, Evans AC. Brain Development Cooperative Group. Cortical thickness correlates of specific cognitive performance accounted for by the general factor of intelligence in healthy children aged 6 to 18. *Neuroimage* 2011;**55**:1443–1453.

Knoester M, Vandenbroucke JP, Helmerhorst FM, van der Westerlaken LA, Walther FJ, Veen S. Matched follow-up study of 5–8 year old ICSI-singletons: comparison of their neuromotor development to IVF and naturally conceived singletons. *Hum Reprod* 2007;**22**:1638–1646.

Leunens L, Celestin-Westreich S, Bonduelle M, Liebaers I, Ponjaert-Kristoffersen I. Cognitive and motor development of 8-year-old children born after ICSI compared to spontaneously conceived children. *Hum Reprod* 2006;**21**:2922–2929.

Leunens L, Celestin-Westreich S, Bonduelle M, Liebaers I, Ponjaert-Kristoffersen I. Follow-up of cognitive and motor development of 10-year-old singleton children born after ICSI compared with spontaneously conceived children. *Hum Reprod* 2008;**23**:105–111.

Lindblom J, Flykt M, Tolvanen A, Vänskä M, Tiitinen A, Tulppala M, Punamäki RL. Complex family system trajectories from pregnancy to child's first year. *J Mar Fam* 2014;**76**:796–807.

Nekkebroeck J, Bonduelle M, Desmyttere S, Van den Broeck W, Ponjaert-Kristoffersen I. Socio-emotional and language development of 2-year-old children born after PGD/PGS, and parental well-being. *Hum Reprod* 2008;**23**:1849–1857.

Nekkebroeck J, Barnes J, Bonduelle M, Wennerholm UB, Ponjaert-Kristoffersen I, Loft A, Sutcliffe AG. International comparison of parenting styles in ICSI, IVF and natural conception families: results from a European study. *Eur J Dev Psychol* 2009;**7**:329–349.

Pandey S, Shetty A, Hamilton M, Bhattacharya S, Maheshwari A. Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis. *Hum Reprod Update* 2012; **18**:485–503.

Plomin R, Asbury K, Dunn J. Why are children in the same family so different? Nonshared environment as decade later. *Can J Psychiatry* 2001; **46**:225–233.

Ponjaert-Kristoffersen I, Tjus T, Nekkebroeck J, Squires J, Verte D, Heimann M, Bonduelle M, Palermo G, Wennerholm U-B. Psychological follow-up of 5-year-old ICSI children. *Hum Reprod* 2004;**19**:2791–2797.

Ramchandani PG, Stein A, O'Connor TG, Heron J, Murray L, Evans J. Depression in men in the postnatal period and later child psychopathology: a population cohort study. *J Am Acad Child Adolesc Psychiatry* 2008;**47**:391–398.

Repokari L, Punamaki RL, Poikkeus P, Tiitinen A, Vilska S, Unkila-Kallio L, Sinkkonen J, Almqvist F, Tulppala M. Ante- and perinatal factors and

child characteristics predicting parenting experience among formerly infertile couples during the child's first year: a controlled study. *J Fam Psychol* 2006;**20**:670–679.

Reynolds CR, Kamphaus RW. *Behavior Assessment System for Children (BASC)*. Circle Pines, MN: AGS, 1992.

Risnes KR, Romundstad PR, Nilsen TI, Eskild A, Vatten LJ. Placental weight relative to birth weight and long-term cardiovascular mortality: findings from a cohort of 31,307 men and women. *Am J Epidemiol* 2009; **170**:622–631.

Rueness J, Vatten L, Eskild A. The human sex ratio: effects of maternal age. *Hum Reprod* 2012;**27**:283–287.

Rutter M. A children's behaviour questionnaire for completion by teachers: preliminary findings. *J Child Psychol Psychiatry* 1967;**8**:1–11.

Skeer MR, McCormick MC, Normand SL, Mimiaga MJ, Buka SL, Gilman SE. Gender differences in the association between family conflict and adolescent substance use disorders. *J Adolesc Health* 2011;**49**:187–192.

Stroud CB, Durbin CE, Wilson S, Mendelsohn KA. Spillover to triadic and dyadic systems in families with young children. *J Fam Psychol* 2011; **25**:919–930.

Sutcliffe AG, Wagenaar K, Huisman J, Cohen-Kettenis PT, Delemarre-van de Waal HA. An overview of studies on early development, cognition, and psychosocial well-being in children born after in vitro fertilization. *J Dev Behav Pediatr* 2008;**29**:219–230.

Vatten LJ, Skjaerven R. Offspring sex and pregnancy outcome by length of gestation. *Early Hum Dev* 2004;**76**:47–54.

Volker J. Paternal involvement: a review of the factors influencing father involvement and outcomes. *TCNJ J Stud Scholar* 2014;**15**:1–8.

Wagenaar K, van Weissenbruch MM, Knol DL, Cohen-Kettenis PT, Delemarre-van de Waal HA, Huisman J. Information processing, attention and visual-motor function of adolescents born after in vitro fertilization compared with spontaneous conception. *Hum Reprod* 2008; **24**:913–921.

Wagenaar K, van Weissenbruch MM, Knol DL, Cohen-Kettenis PT, Delemarre-van de Waal HA, Huisman J. Behavior and socioemotional functioning in 9–18-year-old children born after in vitro fertilization. *Fertil Steril* 2009;**92**:1907–1914.

Wagenaar K, van Weissenbruch MM, van Leeuwen FE, Cohen-Kettenis PT, Delemarre-van de Waal HA, Schats R, Huisman J. Self-reported behavioral and socioemotional functioning of 11- to 18-year-old adolescents conceived by in vitro fertilization. *Fertil Steril* 2011;**95**:611–616.

Weller EB, Kloos A, Kang J, Weller RA. Depression in children and adolescents: does gender make a difference? *Curr Psychiatry Rep* 2006; **8**:108–114.

Zahn-Waxler C, Shirtcliff EA, Marceau K. Disorders of childhood and adolescence: gender and psychopathology. *Annu Rev Clin Psychol* 2008; **4**:275–303.