Looking downstream: a review of the literature on physical and psychosocial health outcomes in adolescents and young adults who were conceived by ART

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BACKGROUND: The use of assisted reproductive technology (ART) is now well established in many countries and the first generations of offspring are reaching maturity. We reviewed the published literature to describe the available evidence about health outcomes in ART-conceived young people who were of an adolescent age or older.

METHODS: The EMBASE, Medline and PsychINFO databases were searched from January 1998 to October 2010. Key inclusion criteria were that the study sample have a mean age of ≥12 years or a mean follow-up period of ≥12 years and were conceived by ART.

RESULTS: Seven publications reported physical health outcomes and 10 reported psychosocial health outcomes in ART offspring. Compared with control groups, some differences in physiological outcomes in relation to growth and development, chronic illness and risk of cancer have been reported. Overall, psychosocial studies of ART-conceived young people indicate that their cognitive function and psychological and social adjustment are similar to that of comparison groups.

CONCLUSIONS: Overall, nine ART-conceived populations of this age group have been studied. Most samples included <300 participants and methodologies varied between studies. Health information on this age group is therefore limited and the clinical significance of the findings remains unclear. Further research focusing on ART-conceived young adults is needed, particularly in relation to neurological health outcomes where no studies have been reported to date.

Key words: assisted reproductive techniques / in vitro fertilization / adolescent development / growth and development / psychological adaptation

Introduction

Events around the time of conception and during fetal life have the potential to influence growth, development and health in later life through the process of reprogramming developmental pathways (Vicens-Calvet et al., 2002; Miles et al., 2005; Barker, 2007). Conception using assisted reproductive technology (ART) involves a number of processes that are very different from a spontaneous conception, such as physical manipulation of gametes and exposure of embryos to hormones and culture medium. Consequently, there is potential for disturbance of normal early developmental processes prompting researchers and clinicians to question whether the health outcomes of ART-conceived people are comparable with that of the general population. Data from developed countries indicate consistent growth in the use of ART (Wang et al., 2006; American Society for Reproductive Medicine and Society for Assisted Reproductive Technology Registry, 2007; Andersen et al., 2008), which further emphasizes the need for assessment of health status in young people conceived from ART.

So far, there have been many investigations of the perinatal outcomes of ART-conceived babies, and these publications present evidence of increased risk of adverse outcomes. Apart from the independent risks
associated with multiple births, ART-conceived singleton babies have significantly higher odds of preterm birth, low and very low birthweight, being small for gestational age and perinatal mortality (Jackson et al., 2004; Schieve et al., 2004; McDonald et al., 2005; Wang et al., 2005). There is also an increased likelihood of an ART-conceived baby having a birth defect compared with a spontaneously conceived baby, even after adjusting for maternal age (Hansen et al., 2005; Reelhuis et al., 2008; Halliday et al., 2010). Beckwith–Wiedemann syndrome, a rare imprinting birth defect, has a higher prevalence among ART-conceived babies, and it is postulated that epigenetic errors associated with ART conception may contribute to an increased risk of other imprinting syndromes, such as Angelman syndrome, and to other ART-related defects that are not presently identified as being epigenetic in origin (Amor and Halliday, 2008). Many imprinting genes are thought to be involved in the regulation of prenatal and post-natal growth and the role of epigenetic alterations in cancer has been well documented (Maher et al., 2003; Feinberg, 2006). There is also evidence that epigenetic mechanisms contribute to changes in developmental pathways from neural and behavioural phenotypes (Horsthemke and Ludwig, 2005; Kerverne and Curley, 2008), emphasizing the importance of studying ART-conceived children throughout development.

Beyond the perinatal period, less is known about the health outcomes of ART-conceived children because many studies are of small samples, are difficult to compare due to different study designs and present findings that are conflicting, ambiguous or have not been replicated. Recent reviews of studies in children up to 12 years of age have summarized the findings on childhood health outcomes after ART conception and despite some differences in nomenclature, six major outcome categories have been reported: growth and development; cognitive development; neurological outcomes; general physical health; childhood cancers and psychosocial outcomes (Alukal and Lipshultz, 2008; Basatemur and Sutcliffe, 2008; Ceelen et al., 2008b; Middelburg et al., 2008; Wagenaar et al., 2008b; Steel and Sutcliffe, 2009; Sutcliffe, 2009; Wannerholm et al., 2009). These reviews concluded that physical growth and development appear to be similar in ART and spontaneously conceived children. Neurological outcomes overall are poorer with higher rates of cerebral palsy and epilepsy, which in turn may be due to increased rates of multiple birth, prematurity and low birthweight of ART-conceived children. In contrast to this, two studies have shown that the risk of autism is not increased when compared with naturally conceived controls (Maimburg and Vaeth, 2007; Hvidtjorn et al., 2010). There is some evidence that ART-conceived children are more likely to be hospitalized, or require more medical treatments and it remains uncertain if they experience more childhood illness or not. The risk of childhood cancers did not appear to be higher in ART-conceived children until very recently when a Swedish study (Kallen et al., 2010) found an increased risk [odds ratio (OR) 1.42, 95% confidence interval (CI): 1.09–1.87]. Lastly, existing studies show that psychological and social wellbeing in ART conceived primary school-aged children is similar to their spontaneously conceived peers and that family functioning and cognitive development is comparable, if not better. In addition to the childhood outcomes summarized in the reviews, there has been one study of thyroid function in children with a mean age of 8.8 years that reported findings of elevated serum thyroid stimulating hormone suggestive of subclinical hypothyroidism in ART children compared with controls (Sakka et al., 2009). There have also been some studies of visual disorders in ART-conceived children (Anteby et al., 2001; Wikstrand et al., 2008). A recent study (Tornqvist et al., 2010) reported no increased risk of ocular malformations but found a slightly increased risk of severe visual impairment in ART-conceived children when compared with controls, and this may have been related to parental risk factors.

There is now a sizeable group of young people who are 12 years and older and conceived by ART. Despite there being no anecdotal reference to overarching problems in these young people, there is a public health obligation to monitor their health and wellbeing at older ages when growth and psycho–social development are further progressed. In addition to the ongoing health effects of conditions diagnosed in early childhood, the health of ART-conceived young people might also be impacted by conditions that go undetected or are not evident until the body matures and the young person is further developed, in particular, pubertal development affecting future fecundity. Furthermore, many parents who have conceived using ART want to know what they can expect of the health and wellbeing of their offspring in the long-term (Fisher-Jeffes et al., 2006; Fisher et al., 2008). As generations of ART-conceived young individuals develop a stronger voice, they too may express a need to understand if the way they were conceived has health implications that may influence their future. The aim of this review is to describe the available studies relating to the health and development of ART-conceived young people who are adolescents or older. Through reviewing studies of this age group, we are hoping to elucidate studies that report on aspects of health that may not have been reviewed previously and address a gap in the literature.

Methodology

Details of the search and selection strategies used to retrieve studies are provided in Table I. Studies that met the inclusion criteria were selected and are reviewed in the results section under the categories of physical health outcomes, psychosocial health outcomes and relevant subheadings. The focus of this review is on outcome studies in ART-conceived individuals of adolescent or older age; therefore, the inclusion criterion was a mean sample age of ≥12 years or a mean follow-up period of ≥12 years. Three publications with sample means of 11.6, 11.9 and 11.11 years, respectively, have been included as their focus was predominantly on adolescent offspring.

Results

The combined searches yielded 1992 publications. Of these, 1812 were not directly relevant or were case studies and 163 were excluded because they did not meet the entry criteria. Two publications were excluded because the exposure was not made explicit and may or may not have included ART (Jensen et al., 2006; Zhu et al., 2009). There were 17 publications that met the inclusion criteria. Table II shows the publications on physical outcomes and Table III shows the publications on psychosocial outcomes.

It is important to note that the 17 publications reviewed only represent nine different populations. Seven of the publications relate to one cross-sectional study of a cohort in the Netherlands, where the authors have reported on physical and psychosocial outcomes (Ceelen et al., 2007, 2008a,c; Wagenaar et al., 2008a, 2009a,b; Ceelen, 2009). Three publications from the UK (Golombok et al.,
The first publication (Ceelen et al., 2007) studied body composition. Findings suggested an increased total body fat in the ART-conceived group but this result was not statistically significant. No group difference was found in bone mineral content. In contrast, statistically significant group differences in some key cardiometabolic indicators were identified in publication 2 (Ceelen et al., 2008a). Systolic and diastolic blood pressure were higher in the ART-conceived group compared with controls, and fasting glucose was higher in the ART-conceived pubertal subgroup (n = 131). Greater growth velocity in infancy was reported for the ART-conceived infants in publication 4 (Ceelen, 2009) but this did not predict higher blood pressure at a later age (mean age of 12.2 years), as might have been expected with ‘catch up growth’. However, weight gain during early childhood (1–3 years, as distinct from infancy) in the ART-conceived children predicted higher blood pressure at a later age, regardless of perinatal outcome. This relationship between childhood growth velocity and blood pressure was not present in the control group.

The findings relating to pubertal development in publication 3 (Ceelen et al., 2008c) were mixed. No significant differences were revealed between the ART and control groups in physical pubertal signs (n = 233) and for the female groups, there were no differences in age at menarche or characteristics of menses (n = 49). A small increase was detected in bone age to chronological age ratio in ART-conceived pubertal females (n = 72) in comparison with the controls and there were slightly higher LH and dehydroepiandrosterone serum hormone levels in a subgroup of 19 pubertal females.

While the Netherlands group have undertaken a carefully executed study with a cohort from one infertility treatment centre, it is unknown 

### Physical health outcomes

**Growth and metabolism**

A group from the VU University Medical Centre in The Netherlands studied different indices of growth and development, and considered the potential consequences of these for health in the short- and long-term (Ceelen et al., 2007, 2008a,c; Ceelen, 2009). The cohort included 233 ART-conceived offspring aged 8–18 years, with a mean age of 12.2 years. Comparisons were made with a matched control group conceived by ‘subfertile’ couples (couples who conceived spontaneously after trying for 12 months or more) to clarify whether ART contributes to the outcomes under study, beyond the effects of subfertility. The cohort was assessed for pubertal stage according to the Tanner score with analysis of additional outcomes within pubertal subgroups. Data were gathered through examination of medical records, survey of parents, and clinical examination and biological testing of the offspring. The findings have been reported in a series of four publications.

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**Table II** Studies reporting physical health outcomes in ART-conceived young adults.

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<tr>
<td>Publication 1 (Ceelen et al., 2007): Cohort A&lt;sup&gt;a&lt;/sup&gt;, The Netherlands</td>
<td>Retrospective cohort: 233 ART-conceived young people (147 pubertal); 233 matched controls conceived from subfertile parents (143 pubertal); mean age 12.2 years; singletons</td>
<td>Height; weight; bone mass; bone density; body fat mass; waist circumference; pubertal stage</td>
<td>No significant differences in height, weight or BMI; DXA&lt;sup&gt;b&lt;/sup&gt; and skinfold measurements suggest total body fat in ART group is increased—although not statistically significant after adjustment; no differences in bone mineral composition</td>
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<td>Publication 2 (Ceelen et al., 2008a): Cohort A&lt;sup&gt;a&lt;/sup&gt;, The Netherlands</td>
<td>Retrospective cohort: 225 ART-conceived young people (131 pubertal); 225 matched controls conceived from subfertile parents (131 pubertal); mean age 12.2 years; singletons</td>
<td>Blood pressure; fasting glucose; fasting insulin</td>
<td>Significantly higher systolic and diastolic BP (mmHg) in ART group than controls, n = 225. (syst. 109 ± 11 versus 105 ± 10, P = &lt;0.001), (diast. 61 ± 7, versus 59 ± 7, P = 0.001). Significantly higher fasting glucose in ART pubertal subgroup than controls, n = 131, (5.0 ± 0.4, versus 4.8 ± 0.4, P = 0.005); no differences in fasting insulin or insulin resistance</td>
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<td>Publication 3 (Ceelen et al., 2008b): Cohort A&lt;sup&gt;a&lt;/sup&gt;, The Netherlands</td>
<td>Retrospective cohort: 233 ART-conceived young people (139 pubertal); 233 matched controls conceived from subfertile parents (139 ARTC pubertal subset); mean age 12.2 years; singletons</td>
<td>Pubertal stage; age at menarche; bone age; sex hormones-luteinizing hormone and dehydroepiandrosterone</td>
<td>No difference in the proportion of pubertal ART-conceived boys, (65 versus 67%, P = 0.69), trend towards difference in the proportion of pubertal ART-conceived girls. (80 versus 73%, P = 0.64), no differences in age at menarche (n = 49); pubertal ART-conceived girls (n = 19) had higher LH&lt;sup&gt;+&lt;/sup&gt; (U/l, 1.5 ± 1.6 versus 0.6 ± 0.7, P = 0.031) and increased DHEAS&lt;sup&gt;d&lt;/sup&gt; [μmol/l, 2.5 (2.0–2.9) versus 1.9 (1.2–2.2), P = 0.017]; pubertal ART-conceived girls (n = 72) had higher BA-C&lt;sup&gt;a&lt;/sup&gt; ratio, (1.04 ± 0.07 versus 1.02 ± 0.08, P = 0.022) and increased BA-CA difference (0.54 ± 0.82 versus 0.18 ± 1 year, P = 0.021)</td>
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<td>Publication 4 (Ceelen, 2009): Cohort A&lt;sup&gt;a&lt;/sup&gt;, The Netherlands</td>
<td>Retrospective cohort: 233 ART-conceived young people; 233 matched controls conceived from subfertile parents; mean age 12.2 years; singletons</td>
<td>Measurements between 0 and 4 years of height, weight, body mass index; Measurements at current age of blood pressure; skin fold thickness; pubertal stage</td>
<td>Late infancy growth velocity of ART children was significantly higher compared with controls; early childhood growth seemed to predict cardiovascular risk factors in ART children i.e. higher blood pressure. Mean inhibin B levels at 14 years, were consistent with reference data for pubertal stage in all but 4/50 boys who were below the 5% percentile; boys born from men with severe oligospermia (n = 32) had comparable inhibin B to those born from men with sperm concentrations above 5 × 10&lt;sup&gt;6&lt;/sup&gt;/ml; mean inhibin B levels increased as expected between 8 and 14 years (n = 25) Clinical depression prevalence was increased (15.9% versus 12.7%); ADD/ADHD prevalence was increased (27.1% versus 5%); binge drinking in females increased (54.6% versus 36.5% NHANES); light, moderate and vigorous activity were increased in males and females compared with NHANES</td>
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<td>(Belva et al., 2010) Belgium</td>
<td>Cross-sectional cohort study; 50 ICSI-conceived boys (25 had longitudinal data from testing at 8 years); compared with population reference data (Andersson et al., 1997); age range 13.6–15.1 years; singletons</td>
<td>Height; weight; pubertal stage; serum inhibit B</td>
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<td>(Beydoun et al., 2010) USA</td>
<td>Cross-sectional: 173 ART-conceived young people; 63% singletons and 37% multiples; mean age; 21.2 years; compared with a population subsample from the National Health and Nutrition Examination Survey 1999–2004 (NHANES)</td>
<td>Self-administered survey of: body size; chronic diseases; cigarette smoking; physical exercise</td>
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whether the mothers in their study were representative of the remain-
der of the source population, the Dutch Omega study (Klip et al., 2001, 2003; de Boer et al., 2003). As was noted, there may have been some selection bias, with over representation of lower education among the non-responding mothers in both the ART and control groups compared with both groups of responding mothers. The samples examined are small and relate to one setting which limits the ability to generalize to other populations of ART-conceived young adults. It is also possible that the differences found are artefacts of multiple testing or may be due to unmeasured confounders. Overall, the significance of the findings of this study are unclear as, although some differences were found between the ART conceived and the control group, there is no evidence yet that these differences have clinical consequences. Because comparisons have been made with offspring conceived from subfertile parents, the results have limited utility for consumers in general. It could also be argued that the comparison group of offspring conceived from parents with a prolonged time to pregnancy are a different population from ART-conceived offspring in terms of parental infertility characteristics, making interpretation of the comparative results complex.

A recent study of testicular function in ART-conceived young males has been reported from Belgium (Belva et al., 2010). Serum inhibin B levels and pubertal stage were measured as a marker for spermatogenesis in a sample of 50 boys aged 14 years who were conceived with ICSI. Half of the sample had taken part in an earlier study at 8 years of age and longitudinal data were available for this group. As with normal pubertal development, mean inhibin B levels increased between 8 and 14 years in comparison with Danish reference data (Andersson et al., 1997). For most of the 14-year-old group (46/50), mean inhibin B levels were consistent with normal reference ranges according to pubertal stage. Boys born to fathers who had severe oligospermia (n = 32) generally had inhibin B levels comparable to those born from men who did not, but it was noted that of the four boys with levels below the reference range, two had oligospermic fathers. This was a small study which has not yet been replicated and requires confirmation from the same sample due to intra-individual variation that occurs when measuring serum inhibin B. A relevant control group would also help with interpretation.

General physical health
There has been one publication from a study of general health outcomes, prevalence of chronic diseases and health risk factors in ART-conceived young adults in the USA (Beydoun et al., 2010). A cohort of 173 young people (63% born as singletons and 37% as one of multiples) aged 18–26 year and conceived from ART completed a cross-sectional survey. Their data were compared with population data, some of which came from the National Health and Nutrition Examination Survey (NHANES) in 1999–2004. The chronic disease profile of ART offspring was found to be similar to the US population, but there was a higher prevalence of clinical depression (15.9% versus 12.7%) and attention deficit/hyperactivity disorder overall (ADD/ADHD) (27.1% versus 3–5%). For ART-conceived individuals, higher physical exercise levels were also reported in both males and females, along with increased binge drinking in females when compared with the NHANES data. The data analysis was conducted on a small sample of mixed plurality although this was said not to confound the findings. Varied data sources used for comparison of the prevalence of chronic conditions made the interpretation of the findings difficult; a matched control group would provide a better comparison. The findings of increased prevalence of ADD/ADHD in ART offspring have not been noted in any previous studies and further research in a larger population of ART-conceived offspring with a satisfactory comparison group would be helpful.

Neurological outcomes
No studies of neurological outcomes in ART-conceived populations with a mean age of 12 years or more were identified. Studies of cognitive development and visual motor function are reported under the psychosocial outcomes section.

Childhood cancer
A study undertaken in Sweden (Kallen et al., 2010) followed up 25 582 ART-conceived offspring to determine the risk of all cancers. The study included all births between 1982 and 2005, and the cohort included a considerable number of young people aged 12 years and older although no age distribution was supplied. ART births in the designated period were identified from all clinics and data were collected through linkage with the Swedish Medical Birth Register and the Swedish Cancer Register. Comparison was made with all other infants in the Medical Birth Register born during the same period, who had survived the perinatal period. A total of 53 cases of cancer were identified among the ART-conceived offspring and after adjustment for year of birth, the OR for childhood cancer was 1.42 (95% CI: 1.09–1.87; P = .01), indicating a statistically increased risk for all cancers. In particular, there were larger than expected numbers of hematologic neoplasms (18 versus 12.3 expected), central nervous...
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<td>Publication 1 (Wagenaar et al., 2008a): Cohort A*, The Netherlands</td>
<td>Retrospective cohort: 233 ART-conceived young people; 233 matched controls conceived from subfertile parents; mean age: ART 12.2 years, controls 12.21 years; singletons</td>
<td>Education level; general cognitive ability (Dutch CITO test); school performance; learning and developmental disorders via parental report</td>
<td>No significant differences were found in school level or ability/performance (n = 74) or in the rate of children with developmental disorders in comparison with the control group. No differences were found in the cognitive functions of information processing and attention in the ART group compared with the control group; visual motor function was lower in ART-conceived people compared with controls but still within normal range. Overall, behaviour and socio-emotional functioning of ART children was normal in comparison with the control group; there was a trend towards less externalizing behaviour in the ART children; in the Teacher Report Form scale there was a trend towards more ART children in the clinical range for withdrawn or depressed behaviour. ART children scored higher than the national mean in all tests and grades (P &lt; 0.0001), and higher than the matched peers for grades 3–11.</td>
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<td>Publication 2 (Wagenaar et al., 2009a): Cohort A*, The Netherlands</td>
<td>Retrospective cohort: 139 ART-conceived young people (pubertal); 143 matched controls conceived from subfertile parents (pubertal); mean age: ART 13.6 years, controls 13.51 years; singletons</td>
<td>Child Behaviour Checklist; Teacher Report Form</td>
<td>No significant differences were found in the behaviour scale of the Child Behaviour Checklist; in the Teacher Report Form scale there was a trend towards more ART children in the clinical range for withdrawn or depressed behaviour. Some slight differences were found in the parent–child relationships that related to the experience of infertility rather than ART specifically (also found in adoptive families) e.g. a trend towards greater indulgence by mothers who had experienced infertility; no differences in socio-emotional functioning were found between offspring from different family types; 76% of ART parents had told their children of their conception. ART families reflected aspects of more positive functioning when compared with donor insemination or naturally conceived families; some over involvement with their children was noted in a small number of parents; the ART-conceived children did not differ from the adoptive or naturally conceived children on any of the measures of psychological adjustment.</td>
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<td>Publication 3 (Wagenaar et al., 2009b): Cohort B*, The Netherlands</td>
<td>Retrospective cohort: 139 ART-conceived young people (pubertal); 143 matched controls conceived from subfertile parents (pubertal); mean age: ART 13.6 years, controls 13.51 years; singletons</td>
<td>Iowa test of basic skills, grades 3–8 Iowa tests of Educational Devt., grades 9–12</td>
<td>ART children scored higher than the national mean in all tests and grades (P &lt; 0.0001), and higher than the matched peers for grades 3–11.</td>
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<td>(Mains et al., 2010) USA</td>
<td>Retrospective cohort 423 ART-conceived children matched controls, naturally conceived children (median of 114 per ART child) Mean age 11.6 years, range 8–17 years Singletons, twins and triplets (analysed separately)</td>
<td>Quality of Parenting Interview (parents); Child and Adolescent Functioning and Environment Schedule (offspring); Expression of Affection Inventory (parents and offspring); Conflict Tactics Scale (parents and offspring); Strengths and Difficulties Questionnaire (offspring); Social Adjustment Inventory for Children and Adolescents (offspring)</td>
<td>Some slight differences were found in the parent–child relationships that related to the experience of infertility rather than ART specifically (also found in adoptive families) e.g. a trend towards greater indulgence by mothers who had experienced infertility; no differences in socio-emotional functioning were found between offspring from different family types; 76% of ART parents had told their children of their conception. ART families reflected aspects of more positive functioning when compared with donor insemination or naturally conceived families; some over involvement with their children was noted in a small number of parents; the ART-conceived children did not differ from the adoptive or naturally conceived children on any of the measures of psychological adjustment.</td>
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<td>Publication 1 (Golombok et al., 2001): Cohort B*, UK</td>
<td>Retrospective cohort: 34 families with ART-conceived children; 49 families with adopted children; 38 families with children conceived from subfertile parents; offspring mean age: 11 years 11 months in all groups</td>
<td>Golombok Rust inventory of Marital State; State-Trait Anxiety Inventory; Beck Depression Inventory; Quality of Parenting Interview; Child and Adolescent Functioning and Environment Schedule; Expression of Affection Inventory; Strengths and Difficulties Questionnaire</td>
<td>No significant differences were found in the rate of children with developmental disorders in comparison with the control group. No differences were found in the cognitive functions of information processing and attention in the ART group compared with the control group; visual motor function was lower in ART-conceived people compared with controls but still within normal range. Overall, behaviour and socio-emotional functioning of ART children was normal in comparison with the control group; there was a trend towards less externalizing behaviour in the ART children; in the Teacher Report Form scale there was a trend towards more ART children in the clinical range for withdrawn or depressed behaviour. No significant differences were found between offspring from different family types; 76% of ART parents had told their children of their conception. ART families reflected aspects of more positive functioning when compared with donor insemination or naturally conceived families; some over involvement with their children was noted in a small number of parents; the ART-conceived children did not differ from the adoptive or naturally conceived children on any of the measures of psychological adjustment.</td>
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<td>Publication 2 (Golombok et al., 2002): UK, The Netherlands, Italy and Spain</td>
<td>Retrospective cohort: 102 families with ART-conceived children; 94 families that conceived with donor insemination; 102 families with naturally conceived children; offspring mean age: 11.9 years</td>
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**Table III** Studies reporting psychosocial health outcomes in ART-conceived young adults.

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system neoplasms (15 versus 8.1 expected), retinoblastoma (2 versus 1.25 expected) and Langerhans histiocytosis (6 versus 1 expected). However, the expected numbers of all cases of cancer in relation to age at onset in the ART-conceived group was similar to the comparison population, although full data were not provided. Controversially, six cases of Langerhans histiocytosis were included as cases. When they were removed from the analysis, the OR decreased to 1.34 (CI: 1.02–1.76). Maternal characteristics did not appear to

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<td>Publication 3 (Golombok et al., 2009): Cohort Bb, UK</td>
<td>Retrospective cohort: 26 ART-conceived young people; 27 adopted young people; 56 young people conceived from subfertile parents; mean age: 18 years</td>
<td>Child and Adolescent Functioning and Environment Schedule; parent—adolescent relationships; Inventory of Peer and Parent Attachment; SCL-90-R; Self-Perception Profile for college students; semi-structured questions about feelings related to ART or adoption</td>
<td>Parent—adolescent relationships did not differ significantly between the ART, adopted or naturally conceived families; Psychological wellbeing showed: no difference in peer relationships; ART adolescents more likely to have displayed physical aggression or been suspended or expelled from school; No difference in psychological problems; ART adolescents perceived themselves as more scholastically competent than adopted group but less so than naturally conceived; 60% of ART adolescents reported they had always known about their ART conception, 40% had been told in late childhood or adolescence. This did not cause them distress</td>
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<td>(Owen and Golombok, 2009): Cohort Bb, UK</td>
<td>Retrospective cohort: 26 ART families (parents only); 26 donor insemination families (parents only); 38 adoptive families (parents only); 63 families with children conceived from subfertile parents (parents only); age of offspring: 17–18</td>
<td>Golombok Rust Inventory of Marital State; Trait Anxiety Inventory; Beck Depression Inventory; Quality of Parenting Interview; interview re level of support with child rearing (maternal only); parents of adolescents separation anxiety scale; Conflict Behaviour Questionnaire</td>
<td>Significantly higher mother—adolescent warmth was found in ART families compared with the adoptive families; there was no difference between the ART and naturally conceived families; donor insemination mothers showed higher expressed warmth when compared with ART mothers; ART mothers showed significantly greater disciplinary indulgence than mothers who naturally conceived but lower indulgence when compared with donor insemination mothers</td>
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<td>(Colpin and Bossaert, 2008), Belgium</td>
<td>Retrospective cohort: 24 ART families; 21 families with naturally conceived children; age range of all offspring: 15–16 years; singletons</td>
<td>Parent—child relationship—Louvain; Adolescent Perceived Parenting Scale; Perceptions of Parents Scales; Parenting Stress Index; Psychosocial Adjustment—Child Behaviour Checklist; youth self-report; Parent Practice and Attitude Towards Disclosure-Questionnaire</td>
<td>No significant differences were found for either self- or adolescent—reported parenting style or stress in ART-conceived adolescents compared with the control group; No differences were found in adolescent’s behaviour between the ART-conceived and the control group; 66% of ART- conceived adolescents (n = 16) had been informed of their ART conception; there did not appear to be a difference in adolescent behaviour between those informed and non-informed about ART conception</td>
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<tr>
<td>(Siegel et al., 2008), Germany</td>
<td>Qualitative interview study: 16 ART-conceived young adults, including one set of twins and one of triplets; age: 19–21 years</td>
<td>Face to face semi-structured interviews, grounded theory analysis</td>
<td>Offspring felt that they were wanted children; they did not perceive themselves to be different and did not perceive negative social effects associated with conception; offspring felt that ART children should be informed of their conception by their parents from an early age</td>
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Cohort Aa, Same cohort in The Netherlands. Cohort Bb, Same cohort in the UK.
influence the cancer risk, although some neonatal characteristics, including preterm birth, birthweight ≥4500 g, being large for gestational age and having low Apgar scores at birth, increased the risk. This study is important due to its length of follow up, but is still insufficiently powered to reach a valid conclusion in relation to the risk of rare childhood cancers in ART-conceived children. Provision of further information on the number of expected cases and the age distribution of the comparison population and the ART population would allow a more thorough assessment.

Psychosocial health outcomes

Cognitive development

Publications 1 and 2 in Table III, by Wagenaar et al. (2008a, 2009a) assessed cognitive development outcomes in ART-conceived young people (8–18 years), and compared them with young people conceived spontaneously by subfertile parents. Publication 1 (Wagenaar et al., 2008a) focused on school functioning within the Dutch education system and the level of schooling achieved and overall performance was found to be the same across the ART and comparison groups for primary school and secondary school stages (n = 233). There was no difference between groups in the proportion of children with developmental disorders. In publication 2 (n = 139), a subgroup of the pubertal children with a mean age of 13.6 years in the ART group and 13.5 years in the control group (Wagenaar et al., 2009a) were assessed for cognitive function, information processing, and attention and visual-motor function. Functioning was found to be the same and normal in both groups. A slightly lower visual motor functioning was observed in the ART-conceived group, which was still within the normal range. It is noted in both publications that the mothers of participants in this study were more educated than the mothers of non-participants. This may have resulted in underreporting of children experiencing learning difficulties or with developmental disorders but would have been a non-differential selection bias.

Another larger study of cognitive development was undertaken in the USA, where the academic performance of ART-conceived children (n = 423) was compared with national population data and a matched peer group (Mains et al., 2010). Results from standardized tests undertaken at grades three to twelve (children aged 8–17 years), in Iowa showed that the ART conceived children performed above average in comparison with the national average and their matched peer group. It was also noted that test scores tended to be lower in children born from multiple gestations but that the difference was not statistically significant. Unfortunately, there was limited information available on the socioeconomic status of the control group other than knowing that they lived in the same geographic area. This may have affected the study findings if they were of a lower socioeconomic group as lower parental education levels were shown to affect offspring test scores. Overall, however, these results are consistent with other findings in younger children.

Psychological adjustment and socio-emotional functioning

In publication 3 by Wagenaar et al. (2009b), behaviour and socio-emotional functioning of a pubertal subgroup of ART children (mean age 13.6 years) was measured through parent and teacher assessment and found to be comparable to the control group (conceived by subfertile parents). There were trends towards fewer externalizing behaviours and increased withdrawn behaviours or depressive symptoms in the ART group as reported by both the parents and teachers. Unfortunately, these findings were not verified with data collected from the offspring.

The ART-conceived young people assessed for psychological adjustment at 11–12 years in the UK and Europe, publications 1 and 2 (Golombok et al., 2001, 2002), did not differ from the adoptive or spontaneously conceived comparison groups on any measure of psychological adjustment at this age. However, in publication 3, which studied the same cohort at 18 years, (Golombok et al., 2009), ART offspring were more likely to have displayed physical aggression or been suspended or expelled from school and perceived themselves as more scholastically competent than the adopted group but less so than the spontaneously conceived group. The study by Colpin and Bossaert (2008) of 15–16 year olds reported no significant differences in behavioural problems amongst the ART-conceived offspring compared with the spontaneously conceived; however, ART boys perceived their fathers as more psychologically controlling than the comparison group. Overall, it is possible that the small differences detected in the above studies may be artefacts of small sample sizes and a few outliers rather than being ART-related.

Parent–adolescent relationships

Several studies examined the parent–adolescent relationship. Colpin and Bossaert (2008) found no significant differences in parenting styles and adolescent behaviours at the age of 15–16 years in ART-conceived young people compared with those conceived spontaneously. In publications 1 and 2 by Golombok et al. (2001, 2002), findings for the 11–12 year old cohorts studied in the UK and Europe were similar although some small differences in parental relationships were noted in the ART-conceived group, including a maternal tendency towards greater disciplinary indulgence of their children in comparison with subfertile parents who had conceived spontaneously. This finding was also apparent in the other comparison group of parents who conceived with donor insemination; hence it was postulated that this may be related to infertility generally, rather than ART specifically. Later on, the parent–adolescent relationship with the same 18-year-old offspring reported by Owen and Golombok (2009) found no difference in ‘mother–adolescent warmth’ between the ART and naturally conceived families. However ART mothers were noted to have a different ‘disciplinary style’ in comparison with mothers who had conceived spontaneously, and the difference in disciplinary indulgence observed in the earlier study was still apparent.

The study by Seigal et al. (2008) provides insight into the attitudes of ART-conceived young adults (19–21 years), towards their ART conception. The study (n = 16) identified positive findings such as cohesive parent–child relationships through feeling wanted by their parents and not perceiving themselves to be different. The young adults also advocated for disclosure of conception at an early age and for parents to repeat the information from time to time, so that children could grow up knowing how they were conceived.

Discussion

This review reveals that worldwide, a total of nine cohorts of ART-conceived young people aged 12 years or more have participated in research to determine their physical and psychosocial well-being. These cohorts range in size but are mostly too small in terms of
power and representativeness to enable firm conclusions about the study findings. Studies of physical outcomes have focused mainly on aspects of growth and development and so far, in the context of an individuals’ development, it would appear that the general health of ART-conceived young people is similar to that of comparison groups. However, physiological differences such as higher blood pressure and fasting blood glucose, increased bone age to chronological age, higher LH and dehydroepiandrosterone sulphate, and increased growth velocity in infancy compared with controls born to subfertile parents have been reported (Ceelen et al., 2007, 2008a,c; Ceelen, 2009). This requires further investigation in much larger samples to determine whether the differences persist and whether they have a longer-term impact on skeletal development, cardiovascular risk or fertility. It is notable that there was only one study relating to ART-conceived young people’s general health and chronic illness and no studies of hospitalizations or neurological outcomes at the time of this review.

Evidence for risk of cancer in ART-conceived young people is limited with one study of sufficient length of follow up, yet still underpowered to detect these rare conditions or specific types of cancer (Kallen et al., 2010). As has been postulated, increased birthweight and respiratory asphyxia have been shown to be associated with an increased risk of childhood cancer and it is feasible that these suboptimal conditions, often associated with ART, may be related to fetal growth factors (Milne, 2008). It is also possible that epigenetic processes occurring around the time of conception may lead to altered expression of imprinted growth factor genes and subsequent potential adverse outcomes (Katari et al., 2009). Our understanding of this will increase as further research in this field is completed.

The publications related to the psychosocial outcomes of ART-conceived young people so far indicate that in general, they are functioning very well cognitively and appear to be psychologically and socially well adjusted. A possible trend towards more withdrawn or symptoms of depression in ART-conceived young people requires further investigation in larger samples (Wagenaar et al., 2009b; Beydoun et al., 2010). Slight differences in the style of parent and adolescent relationships may exist but require further exploration. To date, many of the studies have been small and are potentially biased due to the participation of individuals and families who are functioning well. Future research would benefit from inclusion of more participants from across the socio-economic spectrum, with greater focus on data collection from the young adults themselves.

Research in this field is complex due to the need to collect data from multiple sources in order to determine the effects of ART on outcomes in offspring as distinct from other confounding or mediating factors. It is also fraught by data that are sensitive to technological changes in ART (e.g. freezing, vitrification, ICSI and stimulation) and obstetric care, plus cultural influences that are specific to location (Nygren, 2010). Despite these limitations, all publications are useful in planning future research. Society needs to be informed about the well-being of ART-conceived young people so that they can approach ART in a socially responsible manner. Consequently, governments and the research community must work collaboratively to increase the number and power of studies and boost the accrual of evidence. Studies of chronic illness, cancers and neurological outcomes in particular are needed. While the new generation of ART-conceived young people appear to be faring well, the long-term picture is only beginning to evolve and monitoring of health outcomes must be an ongoing process.

Authors’ roles

C.L.W. conceived the design of the review and conducted the literature search, analysis, interpretation of literature and revision of drafts. J.R.F., K.H. and D.J.A. were involved in design, analysis and interpretation of literature. J.H. co-ordinated the review and contributed to design, analysis and interpretation of literature.

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