Health and functioning of adolescents conceived by assisted reproductive technology

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Objective: To evaluate the general health, mental health, and cognitive ability of assisted reproductive technology (ART)-conceived adolescents.
Design: A nested case-control study within a historic cohort.
Setting: Not applicable.
Patient(s): A total of 253 ART-conceived adolescents born between 1982 and 1993 and 253 matched references according to birth year, gender, and the high-school they attended.
Intervention(s): None.
Main Outcome Measure(s): Medical and psychiatric diagnoses, and cognitive ability recorded at the military preinduction screening (ages 16–17 years) and doctor's appointments throughout the military service.
Result(s): No differences were detected in general and mental health of ART adolescents or cognitive ability, compared with the reference group. Similar results were obtained after stratification for gender and singleton births. The ART adolescents had fewer cases of discharge from military service due to health reasons (4% vs. 8.3%). Follow-up during the military service revealed that male ART adolescents had significantly more doctor's appointments compared with the reference group (23.80 ± 15.59 vs. 19.95 ± 13.79).
Conclusion(s): Our preliminary results provide reassurance that in the long-run health and functioning of ART-conceived adolescents is not compromised. Further studies with larger cohorts are needed to confirm these results. (Fertil Steril® 2017;107:774–80. ©2016 by American Society for Reproductive Medicine.)
Key Words: Assisted reproduction technology (ART), adolescents, follow-up, health

Since the first IVF birth in 1978, increasing numbers of children are being conceived by assisted reproductive technology (ART). In the United States >1% of all infants born every year are conceived through ART, and in Australia and European Nordic countries the percentage increases, reaching almost 5% (1–3). It is estimated that worldwide, >5 million children have been born after assisted conception (4). Concern has been raised regarding the health of ART-conceived offspring. The potential adverse outcomes of conception through ART might be related to intrinsic parental characteristics, perinatal complications, and the assisted reproduction procedures themselves.

It is already known that ART, as well as infertility itself, is associated with an increased risk of fetal malformation (5, 6), perinatal complications, such as preterm delivery, low birth weight, and perinatal mortality (7). Despite the increasing number of reports on the short-term outcomes, there is only limited data on the long-term health and developmental outcomes of ART-conceived offspring. The Developmental origins of health and disease hypothesis suggests that prenatal conditions and exposure to adverse environment at critical stages of development may alter organ development and functioning, resulting in physiological, metabolic, and

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endocrine changes that can predispose offspring to increased susceptibility to disease in later life (3, 8). It has been postulated that periconception and early intrauterine exposures to the altered hormonal milieu in fresh ART cycles, the ex vivo manipulation of gametes and embryos, and the in vitro culture conditions may be the cause of alteration in the genome or epigenome of embryos. Therefore, this could influence the offspring's development with long-term consequences (4, 9).

In light of the dramatic growth in the use of ART and the existing evidence connecting peri-implantation events to postnatal consequences, it is of vital importance to assess the health and functioning of ART children as they reach adulthood. In Israel, all Jewish adolescents undergo a mandatory predraft screening at the ages of 16–17 years to evaluate their eligibility for military service. The current study uses this screening assessment to follow-up on the health of ART-conceived adolescents compared with a matched reference group.

MATERIALS AND METHODS

Sample

All 333 ART-conceived children at the In Vitro Fertilization (IVF) Unit, Sheba Medical Center, Tel Hashomer, Israel, during the period 1982-1993, were evaluated. A computerized database of the children's information was linked to the military screening process database. Military data was obtained for 272 of the ART-conceived offspring. One reference from the general population was then matched to each of the ART-conceived adolescents according to their birth year, gender, and the high school in which they studied. High-school was matched to control for socioeconomic status. Matches were not found for 11 of the ART adolescents, and 8 matched pairs had missing data and were therefore excluded from the analyses. Thus, the final study sample included 253 ART-conceived adolescents and 253 matched references (128 male adolescents). Among the 253 ART offspring, 158 were singletons (79 male adolescents) and 95 were part of multiple deliveries (49 male teenagers).

Military Data

The Israeli Defense Force is a mandatory military service, for all Jewish Israeli adolescents, as well as for some minorities, usually at the ages of 18–21 years for men and 18–20 years for women. One year before conscription to military service, all eligible Israeli adolescents undergo a screening procedure including medical, psychiatric, and cognitive assessments. The medical examination to assess the health status, includes a review of medical records obtained from their primary care physician, a medical history, a physical examination, and when indicated, referral for further assessment (e.g., specialist's examination or functional tests in cases with medical conditions, including asthma). Candidates with severe illness are excluded from military service (10). The psychiatric screening procedure and the cognitive tests are described elsewhere (11, 12).

All data from the recruitment centers, as well as the medical data from the military service, are documented in the soldier's computerized record. All data available during the period 2000-2014 of the recruited soldiers, as well as for those excluded from service were analyzed in this study.

Outcome Measures

Draft board assessment: pulse, diastolic and systolic blood pressure, weight (in kilograms), height (in centimeters), and body mass index (BMI).

Medical and psychiatric diagnoses recorded at the military medical profile: asthma, diabetes, renal disease, migraine, obesity (BMI $\geq$30), heart disease, thyroid disorders, vision problems (keratoconus, cataract, aphakia, glaucoma, strabismus, stereopsis, ptosis, major deficits in vision field, retinitis pigmentosa, color, or night blindness), gastrointestinal disorders, epilepsy, personality disorders, anxiety disorders, mood disorders, and schizophrenia.

Cognitive test at draft board assessment: This is a validated measure of IQ, scoring on a 9-point scale between 10 (low) and 90 (high), with a 10-point increment at each score. The 95th percentile of the total cognitive score was equivalent to an IQ >135, and its correlation with the Wechsler Adult Intelligence Scale total IQ was >0.90 (13).

Exemption from service: yes/no and the medical reason for exemption.

Service medical records: number of doctor's appointments during the military service.

Statistical Analysis

We performed multivariate analysis of variance (MANOVA) to examine the differences between ART-conceived adolescents and matched references on the continuous outcome measures. This analysis was conducted for the entire sample, as well as for male and female adolescents separately. Additional analyses using MANOVA were conducted to examine differences between ART-conceived singletons (n = 158) and their singletons matched references and between ART-conceived singletons and ART-conceived multiples (n = 95). The same analyses were performed for the categorical outcome measures, using logistic regression, where odds ratios (ORs) and 95% confidence of interval (CI) were computed. Under the assumption of $\alpha = 0.05$ and RR = 3 for outcomes of approximately 3% in the general population, sample size of 158 per group will yield approximately 80% power. All analyses were performed using SPSS version 21 (IBM), using two-sided significance level of $P<.05$.

RESULTS

General Health and Cognitive Ability

Comparison between ART-conceived adolescents and matched references revealed no significant differences in health outcomes or cognitive ability (Table 1). Similar results were found when stratifying the entire sample by gender, and when examining only ART-conceived singletons and their

TABLE 1

Health outcomes and cognitive ability in ART adolescents and reference group.

Health outcomes and cognitive ability	ART conceived (n = 253)	Reference group (n = 253)	*P* value/OR [95% CI]
Pulse	74.5 ± 9.4	73.6 ± 9.1	.3
Diastolic blood pressure (mm Hg)	70.4 ± 8.2	69.2 ± 8.4	.1
Systolic blood pressure (mm Hg)	113.3 ± 12.0	114.2 ± 12.3	.3
Height (cm)	168.1 ± 8.6	168.3 ± 8.6	.7
Weight (kg)	61.9 ± 14.5	62.8 ± 12.4	.4
BMI	21.8 ± 4.2	22.1 ± 3.6	.7
Asthma (yes/no)	3.2	2.8	1.15 (0.41–3.21)
Diabetes (yes/no)	0.4	0	0
Renal disease (yes/no)	0	0.8	0
Migraine (yes/no)	5.5	3.2	1.79 (0.74–4.35)
Obesity (yes/no)	5.9	3.6	1.71 (0.73–3.98)
Heart disease (yes/no)	1.2	1.2	1.00 (0.20–5.00)
Thyroid disorders (yes/no)	0.8	0.4	2.01 (0.18–22.29)
Vision problems (yes/no)	37.2	40.3	0.88 (0.61–1.25)
Gastrointestinal disorders (yes/no)	0	0.8	0
Epilepsy (yes/no)	0	0.4	0
Personality disorders (yes/no)	0.8	0.4	2.01 (0.18–22.29)
Anxiety disorders (yes/no)	1.6	1.2	1.34 (0.30–6.04)
Mood disorders (yes/no)	0	0.4	0
Schizophrenia (yes/no)	0	0.4	0
Cognitive test	57.4 ± 15.9	56.0 ± 18.8	.03

Note: Values are presented as mean ± SD or %, unless stated otherwise. ART = assisted reproduction technology; BMI = body mass index; CI = confidence interval; OR = odds ratio.

Fruchter. Health of adolescents conceived by ART. Fertil Steril 2016.

matched reference singletons (Table 2). The ART multiples were significantly thinner (mean, 58.73 kg; SD, 12.40), and had lower BMI (mean, 20.98; SD, 3.58) compared with ART singletons (mean, 63.72 kg; SD, 14.70; mean, 22.27; SD, 4.44; $P=.006$ and $P=.02$, respectively).

Discharge from Military Service

A total of 31 adolescents were found unfit and discharged from military service, 10 in the ART group and 21 in the reference group. The ART-conceived adolescents had significantly fewer cases of discharge from military service due to health reasons compared with the reference group among the entire sample (4% vs. 8.3%, OR = 0.45, 95% CI 0.21–0.99), as well as among males (4.7% vs. 11.7%, OR = 0.37, 95% CI 0.14–0.99) and among male singletons (3.9% vs. 10.4%, OR = 0.35, 95% CI 0.09–1.37). The reasons for exemption from military service in the ART group were disorders of personality and behavior (10), and in the reference group disorders of personality and behavior (16), kidney anomaly (2), overweight and hypertension (1), insect allergy (1), inflammatory bowel disease (1), rheumatic disease (1), and complex regional pain syndrome (1) (some of the exempts had more than one diagnosis).

Doctor's Appointments during Military Service

The ART-conceived men had significantly more doctor's appointments during their military service compared with the reference group (23.8 ± 15.6 vs. 20.0 ± 13.8; $P=.02$). However, no statistically significant differences were found when examining male singletons only (ART = 24.6 ± 16.2 vs. references = 21.8 ± 15.1; $P=.02$).

DISCUSSION

In the present study, the general and mental health status, as well as cognitive ability, of ART-conceived adolescents and matched references was not significantly different, in agreement with previous publications (14–16). The ART-conceived offspring had fewer cases of discharge from military service due to health reasons compared with references, among the entire sample and among males. The ART-conceived male offspring had more doctor's appointments during military service.

There is insufficient knowledge on adolescents born after ART because most of the previous studies are limited to infants or children, and yielded contradictory results. A study by Green et al. (17) found IVF children, especially girls, to be taller than matched references. Because the taller stature was not accompanied by more advanced bone age, the investigators hypothesized that the differences in height were likely to persist into adulthood. Our study does not confirm this hypothesis, showing no difference in height between ART-conceived adolescents and matched references in early adulthood. Other investigators have found advanced bone age in IVF-conceived teenage girls, with no significant differences in anthropometric measurements (18) or increased adiposity (19).

Increased levels of systolic and diastolic blood pressure in ART children were reported in three studies (20–22). Two other studies (23, 24) failed to demonstrate any difference in arterial blood pressure between ART children and controls; although Scherrer et al. (24) reported generalized vascular dysfunction in ART-conceived children. Recently, it was suggested that the ovarian stimulation, as applied in ART, is responsible for the adverse vascular function, as the

TABLE 2

Health outcomes and cognitive ability in ART-conceived singletons and reference group singletons stratified by gender.

	Males			Females		
Health outcomes and cognitive ability	**ART-conceived singletons (n = 77)**	**Reference group singletons (n = 77)**	***P* value/OR [95% CI]**	**ART-conceived singletons (n = 78)**	**Reference group singletons (n = 78)**	***P* value/OR [95% CI]**
Pulse	73.1 ± 9.3	75.8 ± 9.3	.1	74.3 ± 9.6	73.9 ± 8.5	.7
Diastolic blood pressure (mm Hg)	70.7 ± 8.4	70.8 ± 8.4	.9	69.7 ± 8.4	68.0 ± 8.7	.2
Systolic blood pressure (mm Hg)	116.3 ± 11.0	117.3 ± 12.3	.5	109.3 ± 12.8	111.3 ± 13.4	.3
Height (cm)	174.7 ± 6.2	174.1 ± 6.1	.5	163.1 ± 6.5	162.4 ± 6.3	.5
Weight (kg)	69.4 ± 15.2	68.5 ± 13.1	.7	58.2 ± 11.9	56.9 ± 10.2	.5
BMI	22.7 ± 4.9	22.6 ± 4.1	.8	21.8 ± 4.0	21.5 ± 3.3	.6
Asthma (yes/no)	3.9	5.2	0.74 (0.16–3.42)	3.8	2.6	1.52 (0.25–9.36)
Diabetes (yes/no)	1.3	0	0	0	0	0
Renal disease (yes/no)	0	0	0	0	1.3	0
Migraine (yes/no)	6.5	1.3	5.28 (0.60–46.28)	3.8	3.8	1.00 (0.20–5.11)
Obesity (yes/no)	10.4	5.2	2.12 (0.61–7.35)	3.8	2.6	1.52 (0.25–9.36)
Heart disease (yes/no)	2.6	2.6	1.00 (0.14–7.29)	0	0	0
Thyroid disorders (yes/no)	0	0	0	1.3	1.3	1.00 (0.06–16.23)
Vision problems (yes/no)	33.8	40.3	0.76 (0.39–1.46)	39.7	44.9	0.81 (0.43–1.53)
Gastrointestinal disorders (yes/no)	0	1.3	0	0	1.3	0
Epilepsy (yes/no)	0	0	0	0	0	0
Cognitive test (yes/no)	60.53 ± 16.6	56.1 ± 21.1	.1	55.64 ± 13.2	54.7 ± 16.9	.7

Note: Values presented as mean ± SD or %, unless stated otherwise. ART = assisted reproduction technology; BMI = body mass index; CI = confidence interval; OR = odds ratio.

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systolic blood pressure of 4-year olds conceived after conventional controlled ovarian stimulation IVF was significantly higher than in modified natural cycle IVF children (25). Our data demonstrate no difference in heart rate and systolic or diastolic blood pressure between the study and the reference groups.

Previous studies examining the association between ART and asthma have yielded inconsistent results. Consistent with our findings, ART was not found to increase the risk of childhood asthma in some studies (26–30), whereas other studies (31–34) have found an increased risk of asthma and a higher hospitalization rate due to asthma in ART-conceived children. Preschool children have higher asthma morbidity than any other age group (35) and therefore age of examination is critical in interpreting the results. The variation in the follow-up periods, combined with the diverse expression of the disease during different periods of life, may possibly account for the contradicting results. Our results, demonstrating no differences in asthma incidence as ART offsprings enter adulthood, are therefore reassuring.

Researchers have described lower peripheral insulin sensitivity (36), higher fasting glucose levels (21), and higher rates of combined endocrine, nutritional, and metabolic disease including type 1 diabetes (16) among ART offspring compared with the general population. On the other hand, other studies (17, 22, 24, 37) found no difference in various indices of glucose metabolism like fasting insulin or glucose, insulin resistance index, and glucose tolerance. With respect to diabetes, although a growing epidemic has low incidence in young adults and its rare occurrence in our study does not enable us to draw founded conclusions. The incidence of thyroid disorders was low in the study and reference groups. A previous study (38) demonstrated an increase of serum TSH in IVF children. Our study demonstrated no clinical differences in young adults, but again the numbers are too small to draw broad conclusions.

In line with previous studies (20, 26, 39), no difference was found in visual acuity between young adults born as a result of ART and their references. To our knowledge, this study reports the oldest age of visual acuity testing in ART-conceived children.

The ART-conceived offspring had fewer cases of discharge from military service and ART-conceived males consumed more health care services (as expressed by doctor's appointments) compared with their naturally conceived references. The lower rate of discharge from military service in ART-conceived offspring might reflect their good health, as well as high motivation. Higher medical care utilization in younger ART children was reported in previous studies (39–41), in addition to high level of stress among prospective parents undergoing IVF (39). Higher rates of concern might lead ART parents to seek medical care for their offspring more often. Furthermore, the costly and consuming IVF procedure may influence the parents to have higher expectations from their children; a pattern that might be maintained by the child as he or she grows up. We also found ART multiples to be significantly shorter, thinner, and with lower BMI compared with ART singletons. Although consistent with findings in the general population (42, 43), we did not have data on birth height and weight and therefore this finding bears some limitations.

Cognitive ability did not differ between the groups, as well as the prevalence of personality disorders, anxiety disorders, mood disorders, and schizophrenia. Our findings support previous reports of similar mental and cognitive outcomes in ART adolescents and controls (44, 45).

The small number of studies examining health outcomes of ART offspring in adulthood emphasizes the importance of this study. The mandatory predraft evaluations enabled us to estimate the health of ART adolescents, yet eliminating the selection and participation bias. The ART treatments in Israel are part of medical treatments covered for by the state, for every citizen, either Jewish or Arab, and therefore there is no potential bias of socioeconomic status on access to these treatments. All participants were examined regardless of their mode of conception by observers blinded to the conception status. The presence of a matched reference group also contributes to the strength of the study.

However, our research is not without drawbacks. Our sample size (253 ART adolescents) limits the likelihood of detecting group differences for rare medical conditions. Eighteen percent of those conceived by ART were not identified in the military records. Although we did have data on those with no military records, we believe they represent this waived population. We cannot ascertain the number of Arab couples treated during these years in the IVF unit; however, because Arabs represent 20% of the population in Israel, and are exempt from military service, this number is plausible. Another population, which is exempted from military service, are religious orthodox Jewish females, which could also explain the missing military data. The rest of the population is screened at the draft board (or by review of materials in severe cases were subjects cannot personally come in), and therefore even adolescents who were later exempt from service due to severe medical problems will have a military record.

In addition, although the conception status of the reference group was unknown, we assume the majority were spontaneously conceived. In reports from the relevant years, the percentage of ART births of all live births in Israel was approximately 2% (Israel Ministry of Health).

Another disadvantage of the current study is the lack of information regarding the fertility treatment (IVF vs. intracytoplasmic sperm injection [ICSI], fresh vs. frozen-thawed cycles) and the perinatal period (e.g., prematurity and birthweight), therefore limiting adjustments for possible differences in weight and height. Furthermore, we could not control for severity of the medical condition and use of medications. Another limitation of this study is the potential for survivor bias as only living adolescents were recruited. This could lead to an underestimation of the risks of lethal illnesses.

In conclusion, our study aimed to assess the overall general health, mental health, and cognitive ability of

ART-conceived adolescents, irrespective of whether the outcomes were the result of parental characteristics, the procedure itself, or the associated perinatal complications. Physical examination at the ages of 16–17 years, in combination with medical records abstraction and cognitive evaluation revealed reassuring findings. No adverse health outcomes were found in ART adolescents compared with matched references that were spontaneously conceived. Given the high utilization of ART, continuing long-term follow-up of ART-conceived offspring to adulthood is of high importance.

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