

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® 2016; ■:■-■. ©2016 by American Society for Reproductive Medicine.)

Key Words: Assisted reproduction technology (ART), adolescents, follow-up, health

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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 ≥ 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

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