

Serum reproductive hormone levels and ultrasound findings in female offspring after intracytoplasmic sperm injection: first results

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Objective: To compare reproductive hormone levels and antral follicle count in intracytoplasmic sperm injection (ICSI)-conceived offspring and peers born after spontaneous conception.

Design: Single-center study of the reproductive health at the age of 18–22 years in the worldwide oldest cohort of female ICSI offspring.

Setting: University hospital.

Patient(s): A longitudinally followed cohort of singleton women (n = 71) conceived by means of ICSI because of male infertility and a cross-sectionally recruited group of spontaneously conceived women of the same age (n = 81).

Interventions(s): None.

Main Outcome Measure(s): Differences in serum reproductive hormone levels and ultrasound findings.

Result(s): Median levels of antimüllerian hormone (AMH), FSH, LH, and DHEAS were similar between ICSI women and their spontaneously conceived counterparts. Median E₂ levels in ICSI women taking hormonal contraceptives were higher compared with control women. A minority of ICSI women had AMH levels below the 5th or above the 95th percentile, and ICSI women were not more likely to have AMH levels below the 5th percentile or above the 95th percentile compared with control women. Mean follicle count per ovary was similar between the ICSI and control groups. Furthermore, a similar proportion of women had >19 follicles per ovary (ICSI: 20.9%; control: 20.0%). A strong positive correlation between AMH level and mean follicle count per ovary was found.

Conclusion(s): In this cohort of 71 young adult women conceived by means of ICSI because of male infertility in their parents, antral follicle count and circulating reproductive hormone levels, including AMH, FSH, LH, and DHEAS, were found to be similar to results from peers born after spontaneous conception. (Fertil Steril® 2017; ■ : ■ – ■. ©2017 by American Society for Reproductive Medicine.)

Key Words: ICSI, women, offspring, hormones, reproduction, fertility

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Intracytoplasmic sperm injection (ICSI) has become a routine assisted reproductive technology (ART) procedure and has resulted in >2.5 million babies born worldwide (1). Although ICSI was initially performed in couples

with severe male-factor infertility, the indications now also include nonmale infertility (2).

Several studies have described a range of health outcomes between birth and puberty in children born after

various types of ART. However, data regarding the post-pubertal reproductive endocrine function, as a prerequisite of normal reproductive potential, in young adults conceived with the use of ART, are scarce. In a study by Ceelen et al. (3), who described pubertal development in 8–18-year-old IVF-conceived girls and control girls born to subfertile parents, no difference in pubertal stage was found. Interestingly, the authors found higher DHEAS and LH levels in a subgroup of 19 pubertal IVF teenagers compared with control subjects. Furthermore, in ICSI offspring, breast development was less advanced at the age of 14 years

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compared with spontaneously conceived control subjects (4). Despite the growing number of young adults born after IVF and ICSI, their reproductive status in adulthood remains largely unknown. In view of this, we recently described semen characteristics and reproductive hormone levels in 18–22-year-old ICSI-conceived men (5, 6).

Assessment of female reproductive hormone levels typically includes serum analysis of the reproductive pituitary hormones FSH and LH, the ovarian hormone E_2 , and the adrenal hormone DHEAS. Ovarian reserve testing commonly involves a pelvic ultrasound scan to assess antral follicle count (AFC) and analysis of circulating serum antimüllerian hormone (AMH), which has emerged as a reliable marker for ovarian reserve, given its strong correlation with AFC (7).

In the present study, we compared ovarian ultrasound findings and circulating reproductive hormones in the world's oldest ICSI cohort, conceived with the use of ICSI because of (severe) male-factor infertility, with results from spontaneously conceived peers.

MATERIALS AND METHODS

Set-Up and Study Groups

This study is part of a larger project focusing on the metabolic and reproductive health of young adult women and men born after ICSI. This project included the collection of clinical and anthropometric data and blood samples. All participants received written feedback regarding the results of their tests and were offered appropriate counseling, investigation, and follow-up. All participants received an incentive by means of a gift voucher.

Subjects were eligible for inclusion if they were singleton, white, and 18–22 years of age in the study period from March 2013 to April 2016.

Young adult ICSI women, born from 1992 to 1996 after transfer of fresh ICSI embryos with the use of autologous freshly ejaculated sperm, are part of a cohort that has been prospectively monitored since birth. The majority of the women included had been previously clinically assessed. All parents of eligible ICSI offspring in our database ($n = 423$) were sent a letter explaining the background and set-up of the study. Shortly after, these parents were contacted by telephone to explore their and their children's willingness to participate. After parental consent had been obtained, the young adults were approached directly and invited to participate.

From the 208 eligible ICSI families with a female offspring, 154 could be contacted. Because 21 parents decided that "the family" was not interested in participating and 15 couples did not disclose the mode of conception to their child, our invitation actually reached 118 women instead of 154, of whom 71 women (60.2%) agreed to participate. Twenty-two daughters refused without a reason, five had "no time" to participate, four were not willing to undergo the examinations, one was spontaneously pregnant, and one was reluctant about the test results. In 13 cases there was no objection to participate, but the appointment for testing was cancelled and/or no suitable time for testing could be arranged owing to school or work.

A control group of 81 spontaneously conceived peers from 18 to 22 years of age was recruited at college and university campuses by means of oral and written campaigns. Only young women born after spontaneous conception without use of any hormonal stimulation, were eligible as control subjects.

Informed Consent and Ethics Committee

Written informed consents were obtained from all participants enrolled in the study. Participants received written feedback on the test results and were, in case of abnormalities, referred for counseling or further investigation. The study is part of a larger project on reproductive and metabolic health in young adults conceived by ICSI which was approved by the Ethics Committee of the Universitair Ziekenhuis Brussel.

Measurements

Physical examination. Weight and height were measured with the use of standard equipment. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

Pelvic ultrasound scan for AFC was performed by a single operator using a Siemens Acuson X300 equipped with a 2.9–9.7-MHz vaginal probe and 1.4–5.0-MHz abdominal probe. Transvaginal ultrasound was the preferred method for accurate determination of AFC. Transabdominal ultrasound was performed in case transvaginal ultrasound was not possible (virgin participant, anxiety, or refusal). Follicles were counted within the entire ovary. All follicles were counted, but only the number of follicles with diameter ≥ 2 mm and < 10 mm was detailed in the study. Moreover, the left and right ovaries were described in full: size, aspect, follicles of other diameters, number and aspects of cysts, or any other pathology. The mean follicle number per ovary (FNPO) was calculated as the mean value of the number of follicles in the left and the right ovary rounded to the nearest whole number. For the post hoc analysis, a threshold of ≥ 19 follicles per ovary was used to define polycystic ovary morphology (PCOM) according to Dewailly (8).

All examinations (reproductive and metabolic) of all participants were performed on specific days of the week and periods of the year. For this reason, it was not possible to organize ultrasound examinations for days 2–5 of the menstrual cycle. Also, at the time of recruitment, no information on the use of hormonal contraceptives was available. However, this information was registered during clinical exam and used to stratify the results.

Questionnaires. All participants were asked to complete a questionnaire covering a broad range of parameters related to their or their relatives' health status. This included information on lifestyle factors, chronic medication intake (≥ 1 year), chronic illnesses (≥ 1 year), surgical interventions, menstrual cycle, genital abnormalities and their treatment, and hormonal contraceptive drug use (oral, patch, vaginal ring, other). In addition, the family history and educational level of the parents was registered as well as early life factors including in utero exposure to tobacco.

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