Effect of semen quality on human sex ratio in in vitro fertilization and intracytoplasmic sperm injection: an analysis of 27,158 singleton infants born after fresh single-embryo transfer

Mikiko Arikawa, M.D.,[a] Seung Chik Jwa, M.D., Ph.D., M.P.H.,[a,b] Akira Kuwahara, M.D., Ph.D.,[c] Minoru Irahara, M.D., Ph.D.,[c] and Hidekazu Saito, M.D., Ph.D.[a]

[a] Division of Reproductive Medicine, Center of Maternal-Fetal, Neonatal and Reproductive Medicine, National Center for Child Health and Development, Tokyo; [b] SORA no MORI Clinic, Okinawa; and [c] Department of Obstetrics and Gynecology, School of Medicine, University of Tokushima, Tokushima, Japan

Objective: To evaluate the effect of semen quality on human sex ratio in in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI).
Design: Retrospective cohort study.
Setting: Not applicable.
Patient(s): A total of 27,158 singleton infants born between 2007 and 2012 after fresh single-embryo transfer.
Intervention(s): None.
Main Outcome Measure(s): Proportion of male infants among liveborn infants.
Result(s): There were 14,996 infants born after IVF, 12,164 infants born after ICSI with ejaculated sperm, and 646 infants born after ICSI with nonejaculated sperm. The sex ratio of IVF was 53.1% (95% confidence interval [CI], 52.3–53.9); the sex ratio of ICSI with ejaculated and nonejaculated sperm demonstrated as statistically significant reduction (48.2%; 95% CI, 47.3–49.1 and 47.7%; 95% CI, 43.8–51.6, respectively). In IVF, lower sperm motility, including asthenozoospermia (sperm motility <40%), was associated with a statistically significantly lower sex ratio compared with normal sperm (51.0%; 95% CI, 48.6–53.3 vs. 53.4%; 95% CI, 52.5–54.3). In ICSI with ejaculated sperm, there was no association between sperm motility and sex ratio. Sperm concentration was not associated with sex ratio in both IVF and ICSI.
Conclusion(s): In IVF, lower sperm motility was associated with a statistically significant reduction in sex ratio; ICSI with either ejaculated or nonejaculated sperm was associated with a statistically significant reduction in sex ratio regardless of semen quality. (Fertil Steril® 2016;105:897–904. ©2016 by American Society for Reproductive Medicine.)
Key Words: Artificial reproductive technology, nonejaculated sperm, secondary sex ratio, semen analysis

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Reprint requests: Seung Chik Jwa, M.D., Ph.D., M.P.H., Division of Reproductive Medicine, Center of Maternal-Fetal, Neonatal and Reproductive Medicine, National Center for Child Health and Development, 2–10–1, Okura, Setagaya-ku, Tokyo 157–8535, Japan (E-mail: jwa-s@ncchd.go.jp).

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Primary sex ratio (PSR) is defined as the sex ratio at fertilization; secondary sex ratio (SSR) is defined as the sex ratio at birth. Although it is commonly recognized that PSR is male biased [i.e., 51.7%–63% (1)], it was reported recently that PSR is approximately 50% (2). On the other hand, SSR is reported to be almost 51% (i.e., about 105 to 107 male births per 100 female births) in many developed countries, including Japan (3–6). SSR is reported to be affected by biological, environmental, and social factors, such as parental age (7), war (8), earthquakes (9, 10), toxins (11, 12), and economic conditions and policies (13–15).

Since the birth of the first in vitro fertilization (IVF) baby in 1978, the number of pregnancies conceived by assisted reproductive technology (ART) has significantly increased worldwide (16). In Japan, the same trend was seen: 37,953 infants were born after ART in 2012, accounting for 1 in 27 babies born in the country (17–19). A number of factors, including intracytoplasmic sperm injection (ICSI) (20–24) and blastocyst embryo transfer (20, 22, 24–28), are reported to affect SSR in ART. However, when it comes to semen quality, including sperm motility and concentrations, whether it affects SSR in ART remains unclear. To date, no studies have investigated the effect of semen quality on the day of fertilization on SSR in IVF. Furthermore, the number of studies that looked at the effect of semen quality on SSR in ICSI is very limited (29). Based on that background, we investigated the effect of semen quality on sex ratio in IVF and ICSI in Japan using the national ART registry.

MATERIALS AND METHODS

Date Source and Study Sample

All data for analysis were provided by the Japan Society of Obstetrics and Gynecology (JSOG). The data were collected through mandatory reporting from all ART clinics and hospitals using an online system previously described in detail (27, 30–32). The JSOG requires all ART clinics and hospitals to report cycle-specific information, and patients cannot receive administrative subvention without the registration. The database consists of cycle-specific information including patient age, ovarian stimulation protocols used in the treatment, fertilization method in fresh cycle, results of semen analysis for fertilization for ejaculated sperm, and obstetric outcomes, including infant sex. A summary of these data is disclosed on the JSOG Web site annually (18).

Because donor gametes or embryos are prohibited for use in ART in Japan, all the embryos transferred for couples were autologous. Similarly, preimplantation genetic screening for chromosomal aneuploidy, including sex chromosome, is prohibited in Japan. Meanwhile, preimplantation genetic diagnosis (PGD) for specific genetic disorders or recurrent miscarriages due to parental balanced structural chromosomal abnormalities is only allowed after the approval of the institutional review board at each facility and the board of ethics at the JSOG. Between September 2004 and September 2012, there were 671 cycles of oocyte retrieval with PGD in Japan, from which 65 singleton babies were born (33). For this study, data from 2007 to 2012 were used because the Japanese ART registry database was established as an online registration system from 2007 by the JSOG. This study was approved by the institutional review board at the National Center for Child Health and Development and the board of ethics at the JSOG. The data provided by the JSOG did not contain any personally identifiable information.

We included all singleton live births after fresh single-embryo transfer after 22 weeks of gestation or with a birth weight of over 500 g with unknown gestational age. At first, 38,235 infants were eligible for our study. Among those, gamete intrafallopian transfers (n = 35), split IVF or ICSI as the fertilization method (n = 4,958), unknown fertilization method (n = 468), cancellation cycles for embryo transfer (n = 163), unknown or other embryo stage at transfer except early cleavage and blastocyst (n = 1,201), unknown infant sex (n = 310), missing or incomplete data (n = 135) were excluded. For the remaining 30,965 singleton infants with known sex, cases with unknown method of sperm collection (n = 2,587), and missing or incomplete data in either sperm motility or sperm concentration for ejaculated sperm (n = 1,220) were also excluded. Accordingly, 27,158 singleton infants with known semen quality for fertilization or born after ICSI with nonejaculated sperm were included for the analysis.

Semen Quality

Information on total sperm motility and concentration for ejaculated sperm on the day of fertilization was assessed for each cycle. Total sperm motility (%) was expressed as the nearest integer. Sperm concentration ($\times 10^6$/mL) was expressed to two decimal places. Using the information, we defined oligozoospermia as sperm concentration less than 15 million sperm/mL, asthenozoospermia as total sperm motility less than 40%, and oligoasthenozoospermia as a combination of oligozoospermia and asthenozoospermia, according to the World Health Organization classification of subfertility (34). Similarly, total sperm motility and concentration quintiles were used as cutoffs to define groups in the analysis.

Other Variables

Our main outcome was SSR. Other variables included were fertilization method (i.e., IVF or ICSI), embryo stage at transfer (i.e., cleavage-stage or blastocyst), maternal age (categorized in 5-year age groups), year of treatment, infertility diagnosis, and sperm collection method (ejaculated or nonejaculated). In the registry, the embryo stage at transfer can be chosen as cleavage stage or blastocyst. Cleavage stage was defined as embryos before blastocyst, and thus included morula-stage embryos. Infertility diagnosis included tubal factor, endometriosis, antisperm antibody, male factor, unknown factor, and other factor, in which multiple answers were allowed.

Statistical Analysis

Baseline characteristics including maternal age, calendar year and ART cycle-specific parameters (including sperm collection method and semen quality), and delivery outcomes