Effects of assisted reproductive technologies on human sex ratio at birth

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Objective: To investigate the effect of assisted reproductive technology (ART) treatments on the sex ratio of babies born.
Design: Assessment of direct effects of assisted conception through retrospective data analysis on the progeny sex ratio of treated women in the United Kingdom.
Setting: The study uses the anonymized register of the Human Fertilisation and Embryology Authority.
Patient(s): A total of 106,066 babies of known gender born to 76,994 treated mothers and 85,511 treatment cycles between 2000 and 2010 in the United Kingdom.
Intervention(s): Intrauterine insemination, IVF, or intracytoplasmic sperm injection (ICSI).
Main Outcome Measure(s): Sex ratio of babies born.
Result(s): Intrauterine insemination, IVF, and ICSI lead to different sex ratios, highest after IVF (proportion male = mean 0.521 ± confidence interval 0.0056) and lowest under ICSI embryo transfer (0.493 ± 0.0031). In addition, for both ICSI and IVF, transferring embryos at a later stage (blastocyst) results in approximately 6% more males than after early cleavage-stage ET.
Conclusion(s): Because the cumulative number of IVF babies born is increasing significantly in Britain and elsewhere, more research is needed into the causes of gender bias after ART and into the public health impact of such gender bias of offspring born observed on the rest of the population. (Fertil Steril® 2014;101:1321–5. ©2014 by American Society for Reproductive Medicine.)
Key Words: Sex ratio, gender bias, embryo, ART births, IUI, IVF, ICSI

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The prevalence of infertility in European countries is estimated to affect approximately one in seven couples (1). The number of babies born from assisted conception, assisted reproductive technologies (ART), is increasing rapidly: their numbers have quadrupled in the last 20 years, and to date, approximately 5 million babies worldwide have been born after ART (2, 3). In the United Kingdom (UK) the prevalence of infertility is still higher, with one in six couples reported to experience infertility problems (4), and ART births constitute 2%–2.5% of all births in the country (5, 6). Despite these numbers, the impact of ART treatments on the general human population is poorly understood.

There are three commonly used methods of ART. Intrauterine insemination is generally the first line of infertility treatment (1) before proceeding to more invasive procedures such as IVF and intracytoplasmic sperm injection (ICSI) (7). Intrauterine insemination requires a catheter to deposit an appropriate number of washed and resuspended sperm directly into the uterus, thereafter the spermatozoa swim through fallopian tubes toward the ovulated egg (or eggs if ovarian stimulation drugs are used). During IVF or ICSI, cumulus–oocyte complexes are aspirated from the ovaries after an ovarian stimulation regimen. During IVF oocytes are incubated with a known concentration of motile spermatozoa. In contrast, during ICSI the operator selects a single spermatozoon for direct injection into an egg that has been stripped of its cumulus cells using the hyaluronidase enzyme.

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In vitro fertilization or ICSI embryos can then be cultured up to 6 days in vitro and transferred back to the patient according to their number and morphology.

Not only do these three ART methods differ technically, they may differentially affect the sex ratio at birth (8–11), with a general tendency for more males being produced compared with among naturally born offspring. The sex ratio at conception (primary sex ratio), defined according to the numbers of oocytes fertilized by X- or Y-bearing spermatozoa, is difficult to assess (12) and is thus usually unknown. In contrast, the secondary sex ratio (SSR), which may be defined as the proportion of live-born males out of all live births (13), is straightforward to assess, and it is the SSR that most population censuses report in public databases (14–16). At reproductive age, sex ratio bias has the potential to generate substantial public health concerns (8, 12, 17), leading, for instance, to increased socially disruptive behavior, transmission of sexually transmitted diseases, and mental health problems (18–21).

In this study we analyzed the UK national clinical data for SSR of ART children born between 2006 and 2010 as published by the Human Fertilisation and Embryology Authority (HFEA), which regulates licensing and use of human gametes and embryos across the UK (22). Our main aim was to establish whether the SSR of children born in the UK is affected by the ART method used.

MATERIALS AND METHODS

Sample Data

The HFEA anonymized register was accessed for data published between 2000 and 2010. Because the register is anonymized by the HFEA and released as a public document, no ethical approval was needed. The offspring born after 85,511 successful treatment cycles to mothers from across the UK, with a complete dataset on maternal age, ART method used (IUI, IVF, or ICSI), number of eggs collected, number of embryos transferred, and the day of ET until live birth, were included in this study for analysis: 65,438 of the cycles produced single offspring, 19,595 produced twins, 474 produced triplets, and 4 had quadruplets, giving 106,066 babies in total, each of known gender.

Our interest was in evaluating potential influences on the proportion of offspring that were male, that is, the birth (secondary) sex ratio. The variables considered in this research were as follows: ART procedure (IVF, ICSI, or IUI, carried out in 46.00%, 46.60%, and 7.40% of cycles, respectively), mother's age (range, 18–50 years overall, with 55% of mothers aged <35 years and 80% <38 years), numbers of previous IUI and IVF/ICSI cycles, whether gonadotropin stimulation was used, and the year that treatment was carried out. For IVF and ICSI we also evaluated effects of the day of ET (day 1–3 for early [cleaving] stage and day 4–7 for late [blastocyst] stage) and the number or embryos transferred.

Statistical Analyses

The sex ratio of offspring produced from each successful treatment cycle was used as the response variable in statistical analyses with potential influences entered as discrete or continuous explanatory variables within generalized linear models, specifically logistic analyses (using the Genstat statistical package, version 15.1; VSN International). A single analysis on the effects of the ART procedure with all variables was not possible because embryology data do not apply to the IUI procedure.

We used backward elimination procedures and aggregation of factor levels to obtain the parsimonious "minimal adequate model" by model simplification (8, 23–25). We report the percentage of deviance explained (%Dev) as an approximate analogue of r^2. The assumption of quasi-binomially distributed errors (based on empirically estimated scale parameters) was adopted to reduce the probability of type I errors occurring owing to overdispersion (23, 24). Because multiple successful cycles from the same mother (i.e., those mothers who successfully received further treatment to have subsequent children) were initially treated as independent observations, which can promote type I errors, and because the anonymized nature of the HFEA register prevented the entry of maternal identity as a random factor in a generalized linear mixed model (26), we repeated the analysis using the subset of data on only the first successful treatment cycle (n = 76,994). This generated the same conclusions as the full data analysis, thus we formally report results from the larger set of data.

The relative risk (RR; sex ratio after treatment/population sex ratio [27]) that each treatment group generated SSRs different from that of the general population was then calculated from the full set of data and reported with 95% confidence intervals (CIs). All tests were two sided, and $P<.05$ was considered significant.

RESULTS

There were significant sex ratio differences among ART treatment types, but none of the other variables influenced the gender of babies born, nor were there significant interactions between any of the explanatory variables (Table 1). The sex ratios of offspring born to IUI, IVF, and ICSI are shown separately in Figure 1, but sex ratios from IVF and IUI did not differ significantly (aggregation of factor levels [23]: $F_{1,85508} = 2.57$, $P=.109$). Data from ICSI could not be aggregated with either IUI ($F_{1,85508} = 4.05$, $P=.044$) or IVF ($F_{1,85508} = 54.53$, $P<.0001$); the overall result is thus due to significantly lower sex ratios (fewer males) being produced under ICSI than under the other treatment methods.

In vitro fertilization and ICSI embryos were transferred between 1 and 7 days after oocyte aspiration and fertilization, with the number of embryos transferred varying between one and four. Sex ratios were uninfluenced by the number of embryos transferred, but the ratio of male births was higher when ET occurred at later stages of development and, as above, under IVF compared with ICSI (Fig. 2).

The RR of each ART technique and stage of ET was compared with the SSR of the UK general population in 2011 (Fig. 1) as published by the Office of National Statistics (6). The SSR of babies produced from all ART techniques combined was significantly lower than that of the general population (RR 0.9889, 95% CI 0.9827–0.9952, $P=.0005$). Examining only IVF and ICSI showed that each generated