Perinatal outcomes in 6,338 singletons born after intrauterine insemination in Denmark, 2007 to 2012: the influence of ovarian stimulation

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Objective: To study perinatal outcomes in singletons born after intrauterine insemination (IUI) compared with children born after in vitro fertilization (IVF), intracytoplasmic sperm injection, and spontaneous conception (SC), and to assess predictors of poor outcome in singletons born after IUI, exploring the effect of ovarian stimulation.
Design: National cohort study, 2007–2012.
Setting: Danish national registries.
Patient(s): Four thousand two hundred twenty-eight singletons born after insemination with partner semen (IUI-H) and 1,881 singletons born after insemination with donor semen.
Intervention(s): None.
Main Outcome Measure(s): Preterm birth (PTB), low birth weight (LBW), small for gestational age (SGA).
Result(s): Children born after IUI-H had higher risks of PTB, LBW, and SGA vs. SC singletons (adjusted odds ratios [aOR] 1.3; 95% confidence interval (CI), 1.1–1.5; 1.4; 95% CI, 1.2–1.7; and 1.4; 95% CI, 1.2–1.6), respectively. Compared with IVF, risk of SGA was similar, but risks of PTB and LBW were lower (aOR 0.6; 95% CI, 0.5–0.8; and 0.8; 95% CI, 0.6–0.9). Compared with intracytoplasmic sperm injection, no differences were found. For children born after IUI with donor semen, results were similar to those for IUI-H. Risks of LBW and SGA were higher in IUI singletons born after ovarian stimulation with clomiphene citrate, compared with natural-cycle IUI (aOR 1.5; 95% CI, 1.1–2.1 and 1.6; 95% CI, 1.1–2.4). Treatment with follicle-stimulating hormone vs. natural-cycle IUI did not seem to affect perinatal outcomes.
Conclusion(s): Singletons born after IUI had higher risk of adverse perinatal outcomes compared with SC children, similar to ICSI, but favorable outcomes compared with IVF. Stimulation with clomiphene citrate was associated with higher risk of SGA compared with natural-cycle IUI, but follicle-stimulating hormone treatment did not seem to be associated with adverse outcomes.
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Key Words: Intrauterine insemination, perinatal outcome, clomiphene citrate, ovarian stimulation, small for gestational age, preterm birth

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Intrauterine insemination (IUI) is widely used in Denmark and accounts for more than half of all fertility treatments conducted nationally (1). In Denmark, use of assisted reproductive technology (ART) has been recorded in the national ART register since 1994, and registration of IUI treatments has been mandatory since 2007. In Europe, reproductive technologies are recorded in national registers in 34 countries, whereas data on IUI are only available from 21 countries (2). A limited number of studies have investigated perinatal outcomes in children born after IUI and found increased risks compared

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with spontaneously conceived (SC) children (3–6). A few small, predominantly clinic-based studies have compared IUI to in vitro fertilization (IVF), and the results point toward either comparable or lower risks of adverse perinatal outcome in IUI vs. IVF (7–9).

Increased risks of adverse perinatal outcome in singletons born after ART compared with SC children have been observed in several descriptive studies (10). The slightly poorer outcomes in ART singletons are linked to maternal age and primiparity, subfertility, vanishing twins, fresh vs. frozen embryo transfer, and blastocyst transfer. Moreover, ovarian stimulation and laboratory procedures have also been suggested as explanatory factors (10–13). Understanding the relative contribution of the various factors is important for minimizing the effect of iatrogenic causes and for assessing the safety of fertility treatments and the continuous advancements in assisted reproduction. Considering the potential influence of culture media, culture time, and other laboratory factors in ART, a study on infant outcome after IUI may be suitable for assessing the effect of parental factors and ovarian stimulation.

This study, based on a national cohort of children born after IUI, aims to assess the obstetric and perinatal outcomes in children born after IUI compared with children born after IVF, those born after intracytoplasmic sperm injection (ICSI), and those who were SC. Further, we aim to explore predictors of poor perinatal outcome in children born after IUI, assessing whether outcomes are influenced by ovarian stimulation, cause of infertility, and use of partner or donor semen.

MATERIALS AND METHODS

The Danish ART Register

All initiated treatment cycles are recorded in the mandatory ART register, and through the personal social security number, data were cross-linked to the medical birth register and hospital discharge register, to obtain information on live births as well as obstetric and perinatal complications. The ART register includes data on body mass index (BMI), smoking status, cause of infertility, partner/donor semen, and type of medication used during fertility treatment.

All children born after IUI in Denmark from 2007 to 2012 were identified in the Danish ART register and cross-linked to the medical birth register (n = 7,900: singletons n = 6,338; twins n = 1,517; triplets n = 45). Two control cohorts of all children born after IVF (singletons n = 4,135) and ICSI (singletons n = 3,635), 2007–2012, were also identified in the 2 registers (ART and medical birth register). Children born after oocyte donation, preimplantation genetic diagnosis, percutaneous epididymal/testicular sperm aspiration, and frozen embryo transfer were excluded. The third control group, which consisted of all SC singletons, 2008–2011 (n = 229,749), were identified in the medical birth register.

We excluded SC children born in 2007 and 2012 for the following reasons: in 2007, the ART register was converted from paper-based registration to online registration, and during 2007, the electronic data registration was incomplete, in particular the IUI cycles, as the registration of IUI cycles was initiated concomitantly with introduction of the electronic register. Hence, some of the treatment cycles in 2007 were not registered, and some of the children conceived after fertility treatments in 2007 appear as SC children. Thus, to avoid bias, we excluded SC children from this year. The reason for excluding the year 2012 in the SC children cohort was that the ART registrations for 2012 were not yet completed at the time data were extracted from the registers, which again categorized children conceived after fertility treatment into the SC cohort.

Data on cause of infertility, use of partner/donor semen, duration of infertility, and type of medication used during fertility treatment were retrieved from the IVF register. Data on perinatal outcomes were extracted from the medical birth register. Diagnoses obtained from the hospital discharge register were: hypertensive disorders of pregnancy, placenta previa, cesarean section, induction of labor, and admittance to a neonatal intensive care unit.

According to Danish legislation, studies based solely on register data and with no personal contact/involvement of the participants do not require approval from an ethical committee. The study was approved by the Danish Data Protection Agency (CVR-FSEID 00000303) and the National Board of Health.

Statistics

The differences between study and control populations were analyzed in SPSS, version 15.0. Statistical significance was defined as $P<.05$. Differences of the means of continuous parametric data were analyzed with the use of analysis of variance and Bonferroni correction. For nonparametric data, medians and interquartile ranges (IQR) were reported, and differences were analyzed in SPSS with the Kruskal-Wallis test. The χ^2 test and Bonferroni correction were used to compare distributions between 2 groups.

The risks of being small for gestational age (SGA) and large for gestational age (LGA) were calculated in relation to the 10th percentile by Marsal's formula with the use of birth weight, child gender, and standard intrauterine growth curves for Scandinavia (14). Multivariate logistic regression analyses were performed to estimate risks of preterm birth (PTB, gestational age <37 weeks), low birth weight (LBW, birth weight <2,500 grams), SGA, and LGA. The analyses were adjusted for maternal age, parity, child gender, year of birth, smoking, maternal BMI, elective cesarean section, and induction of labor. All stillbirths and children with missing information on gestational age or birth weight, as well as children with a gestational age of <140 days or >308 days, and children with a birth weight <200 grams or >9,000 grams were excluded in the analyses of birth weight, gestational age, LBW, PTB, and SGA/LGA. In the stratified analysis, use of ovarian stimulation in the cycle leading to birth is assessed. Natural cycle IUI was defined as those who received no treatment with clomiphene citrate (CC) or follicle-stimulating hormone (FSH)–containing preparations. However, approximately 44% of women in the