Effect of maternal age on maternal and neonatal outcomes after assisted reproductive technology

Anna Lena Wennberg, M.D., Ph.D.,[a,b] Signe Opdahl, M.D., Ph.D.,[c,d] Christina Bergh, M.D., Ph.D.,[a] Anna-Karina Aaris Henningsen, M.D.,[e] Mika Gissler, Ph.D.,[f] Liv Bente Romundstad, M.D., Ph.D.,[c,d,g] Anja Pinborg, M.D., Ph.D.,[h] Aila Tiitinen, M.D., Ph.D.,[i] Rolv Skjærven, Ph.D.,[j,k] and Ulla-Britt Wennerholm, M.D., Ph.D.[a]

[a] Department of Obstetrics and Gynecology, Institute for Clinical Sciences, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden; [b] Nordic IVF Center Göteborg, Gothenburg, Sweden; [c] Department of Public Health and General Practice, Norwegian University of Science and Technology, Trondheim, Norway; [d] Central Norway Regional Health Authority, Stjørdal, Norway; [e] Fertility Clinic, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [f] National Institute of Health and Welfare, Helsinki, Finland; [g] Spiren Fertility Clinic, Trondheim, Norway; [h] Department of Obstetrics and Gynecology, Hvidovre Hospital, Institute of Clinical Medicine, Copenhagen University Hospital, Copenhagen, Denmark; [i] Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [j] Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway; and [k] Medical Birth Registry of Norway, National Institute of Public Health, Bergen, Norway

Objective: To compare the effect of maternal age on assisted reproductive technology (ART) and spontaneous conception (SC) pregnancies regarding maternal and neonatal complications.
Design: Nordic retrospective population-based cohort study. Data from national ART registries were cross-linked with national medical birth registries.
Setting: Not applicable.
Patient(s): A total of 300,085 singleton deliveries: 39,919 after ART and 260,166 after SC.
Intervention(s): None.
Main Outcome Measure(s): Hypertensive disorders in pregnancy (HDP), placenta previa, cesarean delivery, preterm birth (PTB; <37 weeks), low birth weight (LBW; <2,500 g), small for gestational age (SGA), and perinatal mortality (≥28 weeks). Adjusted odds ratios (AORs) were calculated. Associations between maternal age and outcomes were analyzed.
Result(s): The risk of placenta previa (AOR 4.11–6.05), cesarean delivery (AOR 1.18–1.50), PTB (AOR 1.23–2.19), and LBW (AOR 1.44–2.35) was significantly higher in ART than in SC pregnancies for most maternal ages. In both ART and SC pregnancies, the risk of HDP, placenta previa, cesarean delivery, PTB, LBW, and SGA changed significantly with age. The AORs for adverse neonatal outcomes at advanced maternal age (>35 years) showed a greater increase in SC than in ART. The change in risk with age did not differ between ART and SC for maternal outcomes at advanced maternal age.
Conclusion(s): Having singleton conceptions after ART results in higher maternal and neonatal outcome risks overall, but the impact of age seems to be more pronounced in couples conceiving spontaneously. (Fertil Steril® 2016;106:1142–9. ©2016 by American Society for Reproductive Medicine.)
Key Words: Assisted reproductive technologies, ART, spontaneous conception, maternal age, maternal complications, neonatal complications

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Reprint requests: Anna Lena Wennberg, M.D., Ph.D., Nordic IVF Center Göteborg, Odinsgatan 10, 411 03 Gothenburg, Sweden (E-mail: annalena.wennberg@gbgkk.se).

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Many women today delay childbirth until their fourth and fifth decades. According to Nordic Perinatal Statistics the mean age at first delivery increased from 23–24 years in 1975 to 28–29 years in 2012 in Denmark, Norway, and Sweden (1), and the same trend is observed in most high-income countries. The reasons for postponement of childbearing are probably multifactorial and include better access to contraception, longer education, later marriage, higher career goals, desire for financial stability, and other social factors, as well as advances in assisted reproductive technologies (ART). It is well established that fecundity decreases rapidly with age >35 years and delayed motherhood increases the demand for reproductive assistance. Meanwhile, the introduction of new technologies, such as oocyte donation and fertility preservation through oocyte cryopreservation, to counteract the age-related decline of fertility (also called social freezing) makes pregnancy possible even at a very advanced maternal age. Yet, a higher maternal age increases the risk of adverse maternal and neonatal outcomes. The risk of preeclampsia and gestational diabetes in women ≥45 years of age is two to three times the risk for younger women (2–4). There is a higher risk of preterm birth (PTB), low birth weight (LBW), and perinatal mortality associated with higher maternal age, as well as an increased risk of operative delivery (2, 3, 5). Many large studies have also described the maternal and neonatal risks related to ART (6–8). Although it is known that ART increases the risk of maternal complications such as hypertensive disorders in pregnancy (HDP), placenta previa, and cesarean delivery, as well as the risk of poor neonatal outcome, little is known about the interplay between age-related and ART-related risks. Theoretically, advanced maternal age in combination with ART could increase the risks even further. The Committee of Nordic ART and Safety (Conartas) cohort comprises all children born after ART in the Nordic countries from 1982 to 2007 and gives a unique opportunity to study maternal risks and neonatal outcome of ART pregnancies at different maternal ages and compare them with spontaneously conceived (SC) pregnancies (9).

The aim of the present study was to estimate the effect of maternal age on maternal and neonatal complications in ART compared with SC. In addition, we studied the effect of maternal age separately within ART and SC pregnancies.

MATERIALS AND METHODS

The Conartas study population is a population-based cohort comprising data on all deliveries after ART in Sweden, Denmark, Finland, and Norway from 1982 to 2007. Data were obtained from each country's national ART and medical birth registry and combined as described in detail previously (9). Briefly, the IVF clinics in the Nordic countries are responsible for reporting to national ART registries, and this reporting is mandatory. A personal identification number given to all citizens allows linkage to the national medical birth registries. A comparison group, consisting of four control subjects after SC, was selected for every ART child. In each country, matching was performed for parity (primiparity or parity >1) of the mother and year and month of birth of the child. The comparison group comprised 332,915 SC singletons (including all of the control subjects for ART singletons and multiples). In this study, only fresh cycles with own oocytes and singleton ART pregnancies from the Conartas cohort were included. Data from Finland could not be included in the present study, because it was not possible to discriminate between fresh and frozen-thawed cycles in the Finnish cohort. We excluded pregnancies with missing information (n = 4,460) and pregnancies with impossible or extreme values on gestational age (<22+0 weeks or ≥45+0 weeks; n = 319) or birth weight (≥7,000 grams; n = 846). Pregnancies with year of birth before 1988 were excluded owing to the very small numbers. Only women aged 20–46 years were included owing to the small number of reported ART births in women <20 years of age and no reported ART births in women >46 years of age. Thus, the present study population consisted of 39,919 ART singleton deliveries and the control group of 260,166 singleton deliveries after SC. In total, 300,085 singleton deliveries were included in the study.

For maternal complications, we used the International Classification of Diseases, Ninth (ICD 9; 1987–1996) and Tenth (ICD 10; 1997–2007) Revisions. The maternal complications analyzed included HDP (chronic hypertension with superimposed preeclampsia, gestational hypertension, and preeclampsia; ICD 9: 642 D–H, X; ICD 10: O11, O13–O16), placental abruption (ICD 9: 641 C; ICD 10: O45), placenta previa (ICD 9 641 A–B; ICD 10: O44), and cesarean delivery. Neonatal outcome comprised PTB <37 weeks, PTB <32 weeks, LBW <2,500 g, very low birth weight (VLBW; <1,500 g), small for gestational age (SGA; >2 standard deviations) below the gestational and sex-specific Swedish growth standard (10), macrosomia (birth weight ≥4,500 g), and perinatal mortality. Perinatal mortality was defined as live birth with death from day 0 to 6 and stillbirth, both restricted to pregnancies of ≥28+0 weeks.

Information on maternal and neonatal complications was obtained from each country's national medical birth registry. For ART pregnancies, information on date of embryo transfer, fertilization method (in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), or combination of IVF and ICSI), and cryopreservation of embryos was obtained from the national ART registries.

For SC pregnancies, gestational age was defined according to ultrasound investigation performed in the second trimester or from the date of the last menstrual period if ultrasound had not been performed. In ART pregnancies, gestational age was calculated from the date of oocyte retrieval or from ultrasound examination if the date of oocyte retrieval was not available.

Permission from Ethics Committees

The study was approved by the Data Protection Agency and the authorities responsible for the relevant registers in each participating country. Permission from ethics committees was given in Norway (REK 2010/1909-11) and Sweden (Regional Ethics Committee at the University of Gothenburg: Dnr 023-09, T431-09), and in Denmark permission was not required.