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

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/10957-effect-of-maternal-age-on-maternal-and-neonatal-outcomes-after-assisted-reproductive-technology

Received March 21, 2016; revised May 22, 2016; accepted June 10, 2016; published online July 9, 2016.
A.L.W. has nothing to disclose. S.O. has nothing to disclose. C.B. has nothing to disclose. A.-K.A.H. has nothing to disclose. M.G. has nothing to disclose. L.B.R. has nothing to disclose. A.P. has nothing to disclose. A.T. has nothing to disclose. R.S. has nothing to disclose. U.-B.W. has nothing to disclose.
Supported by Nordforsk and through a fund for research and the education of doctors (ALFGBG-70 940). The Conartas steering committee received travel and meeting grants from the Nordic Federation of Societies of Obstetrics and Gynecology.
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).

Fertility and Sterility® Vol. 106, No. 5, October 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.06.021

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.

Statistical Analyses

The association between maternal age and a binary outcome was analyzed by means of logistic regression with the use of generalized estimating equations (GEE) for estimation and taking correlations within individuals into account. To allow for the effect of age to vary with age, piecewise logistic regression was used. Breakpoints where the regression coefficients for age were allowed to change were at 30, 35, and 40 years. With this model, the odds ratio (OR) with age was assumed to be constant within the age intervals <30, 30–35, 35–40, and >40 years but was allowed to change between intervals. Owing to the small number of events for perinatal mortality in women >40 years of age, the breakpoint at 40 years was excluded in the models for this outcome, resulting in models assuming a constant OR with age ≥35 years. The OR of event for ART versus SC at selected ages 30, 35, 40, and 45 years was estimated. Overall tests for the effect of age and for difference between ART and SC were carried out as contrasts of model parameters. Interaction analyses were carried out to test whether the OR with age for advanced maternal age >35 years differed between ART and SC. All analyses were adjusted for parity (continuous), year of birth (continuous), offspring, sex, and country. All plots of predicted risk as functions of maternal age were evaluated with parity and year of birth set to the median values in the cohort and with the use of weights on offspring sex and country according to the distribution in the cohort. All tests were two tailed and conducted at a 5% significance level, interpreting individual tests as significant only if the corresponding overall test was significant. Parameter estimates and contrasts of parameters were tested by means of Wald tests with the use of the empirical covariance matrix. All analyses were conducted with the use of SAS System for Windows, version 9.4.

RESULTS

In total, 39,919 ART and 260,166 SC singleton pregnancies (35,571 women in ART and 237,965 women in SC) were analyzed. Baseline characteristics are described in Table 1. The study flow chart is presented in Supplemental Figure 1 and the maternal age distributions of ORs in Supplemental Figures 2–12 (available online at www.fertstert.org). The mean maternal age for ART was 33.3 years (SD 4.0) and for SC 28.8 years (SD 4.4). For all ages combined, the occurrence of adverse outcomes was higher in ART than in SC pregnancies. This applied to both maternal outcomes (HDP, placental abruption, placenta previa, and cesarean delivery) and most neonatal outcomes (PTB <37 and <32 weeks, LBW, VLBW, SGA, macrosomia, perinatal mortality ≥28 weeks; Table 2).

Maternal Outcomes

At 25 and 30 years of age, the risk of HDP was higher in ART than in SC pregnancies (adjusted ORs [AORs] 1.42 and 1.13, respectively). In ART there was a significant increase in HDP from maternal age 35 to 40 years (AOR 1.35) and in SC pregnancies up to 40 years of age (AORs 1.04–1.51). The change in risk of HDP with age did not differ between ART and SC at maternal age >35 years (P=.19, test for interaction; Tables 3 and 4; Supplemental Fig. 2).

TABLE 1

Baseline characteristics.

Variable	ART (n = 39,919)	SC (n = 260,166)	*P* value
Country			<.0001
Sweden	19,445 (48.7%)	123,389 (47.4%)	
Denmark	12,440 (31.2%)	74,512 (28.6%)	
Norway	8,034 (20.1%)	62,265 (23.9%)	
Year of birth			
1988–1992	1,602 (4.0%)	12,282 (4.7%)	
1993–1997	5,996 (15.0%)	42,203 (16.2%)	
1998–2002	12,613 (31.6%)	87,844 (33.8%)	
2003–2007	19,708 (49.4%)	117,837 (45.3%)	
Maternal age, y	33.3 ± 4.0	28.8 ± 4.7	<.0001
Maternal age, y (in categories)			
<25	1,019 (2.6%)	66,647 (25.6%)	
25 to <30	8,694 (21.8%)	102,497 (39.4%)	
30 to <35	17,851 (44.7%)	67,186 (25.8%)	
35 to <40	11,267 (28.2%)	21,081 (8.1%)	
40 to <45	1,082 (2.7%)	2,721 (1.0%)	
≥45	6 (0.0%)	34 (0.0%)	
Parity	1 (1; 2)	1 (1; 2)	<.0001
Parity (in categories)			
1	28,734 (72.0%)	177,667 (68.3%)	
2	9,333 (23.4%)	52,275 (20.1%)	
3	1,398 (3.5%)	21,413 (8.2%)	
4	341 (0.9%)	5,961 (2.3%)	
≥5	113 (0.3%)	2,850 (1.1%)	
Offspring sex			.092
Male	20,624 (51.7%)	133,233 (51.2%)	
Female	19,295 (48.3%)	126,933 (48.8%)	
Birth weight, g	3,415 ± 643	3,507 ± 577	<.0001
Gestational age, d	276.3 ± 16.3	278.9 ± 13.7	<.0001
ART procedure			
Fresh IVF	26,155 (65.5%)	0 (0.0%)	
Fresh ICSI	13,720 (34.4%)	0 (0.0%)	
Unknown or combination	44 (0.1%)	0 (0.0%)	

Note: Categoric variables are presented as n (%), continuous variables as mean ± SD, and parity as median (interquartile range). For comparisons between groups, Fisher exact test was used for dichotomous variables, chi-square test nonordered categoric variables, and *t* test for continuous variables. ART = assisted reproductive technologies; SC = spontaneous conception.

Wennberg. Age and obstetrical outcome in ART. Fertil Steril 2016.

The risk of placental abruption was significantly higher in ART than in SC pregnancies at all ages except 45 years of age (AORs 1.55–2.69). The risk of placental abruption did not change by age in ART, whereas the risk increased from 30 and 35 years in SC pregnancies (AOR 1.26). The change in risk of placental abruption with age did not differ between ART and SC at advanced maternal age >35 years (P=.93, test for interaction; Tables 3 and 4; Supplemental Fig. 3).

The risk of placenta previa was higher in ART than in SC pregnancies at all ages except 45 years of age (AORs 4.11–6.05). The risk of placenta previa in ART increased with age up to 30 years of age (AOR 1.84) and up to 35 years of age in SC pregnancies (AORs 1.72 and 1.88, respectively). The change in risk of placenta previa with age did not differ between ART and SC at maternal age >35 years (P=.92, test for interaction; Tables 3 and 4; Supplemental Fig. 4).

The risk of cesarean delivery was higher in ART than in SC pregnancies at all ages except 45 years of age (AORs 1.18–1.50). There was a significant increase in the risk of cesarean delivery with increasing age in both ART (AORs 1.17–

TABLE 2

Maternal and neonatal outcomes, n (%).

Variable	ART (n = 39,890)	SC (n = 245,600)	*P* value
Hypertensive disorders in pregnancy	2,281 (5.7%)	11,551 (4.7%)	<.0001
Placental abruption	347 (0.9%)	1,129 (0.5%)	<.0001
Placenta previa	635 (1.6%)	599 (0.2%)	<.0001
Cesarean section	10,013 (25.1%)	40,092 (16.3%)	<.0001
Preterm birth <37 wk	3,512 (8.8%)	13,819 (5.6%)	<.0001
Preterm birth <32 wk	699 (1.8%)	2,111 (0.9%)	<.0001
Low birth weight <2,500 g	2,626 (6.6%)	9,607 (3.9%)	<.0001
Very low birth weight <1,500 g	633 (1.6%)	1,827 (0.7%)	<.0001
Small for gestational age	2,180 (5.5%)	10,477 (4.3%)	<.0001
Birth weight ≥4,500 g	1,225 (3.1%)	8,574 (3.5%)	<.0001
Perinatal mortality ≥28 wk	229 (0.6%)	1,016 (0.4%)	<.0001

Note: For comparison between groups, Fisher exact test was used. ART = assisted reproductive technologies; SC = spontaneous conception.

Wennberg. Age and obstetrical outcome in ART. Fertil Steril 2016.

1.85) and SC (AORs 1.36–1.86) pregnancies across the entire range of maternal age. The change in risk of cesarean delivery with age did not differ between ART and SC at maternal age >35 years (P=.80, test for interaction; Tables 3 and 4; Supplemental Fig. 5).

In general, the results of the unadjusted analyses were similar to the results of the adjusted analyses (Supplemental Tables 1 and 2, available online at www.fertstert.org).

Neonatal Outcomes

The risk of PTB (<37 weeks and <32 weeks) was significantly higher in ART than in SC singletons (PTB <37 weeks: AORs 1.23–2.19; PTB <32 weeks: AORs 1.68–3.20) except at maternal age 45 years for PTB <37 weeks and at 40 and 45 years for PTB <32 weeks. The risk of PTB (<37 weeks and <32 weeks) changed by age in both ART and SC pregnancies, the risk decreasing significantly in ART up to 30 years of age but not changing after 30 years. The risk of PTB (<37 weeks and <32 weeks) increased in SC pregnancies with maternal age from 30 to 40 years (PTB <37 weeks: AORs 1.15 and 1.27, respectively; PTB <32 weeks: AORs 1.26 and 1.45, respectively). The change in risk of PTB <37 weeks with age was significantly different between ART and SC pregnancies in women of maternal age >35 years (P=.043, test for interaction), with an increased risk seen for SC >35 years, but not for ART pregnancies. The change in risk of PTB <32 weeks with age did not differ between ART and SC pregnancies at maternal age >35 years (P=.36, test for interaction; Tables 3 and 4; Supplemental Figs. 6 and 7).

The risk of LBW and VLBW was significantly higher in ART than in SC singletons in all ages up to maternal age 40 years (LBW: AORs 1.44–2.35; VLBW: AORs 1.67–3.44). The risk of LBW and VLBW in both ART and SC singletons changed with maternal age. The risk decreased significantly in ART up to 30 years of age but did not change after 30 years. In SC singletons, the risk of LBW increased with maternal age from 30 to 40 years (AORs 1.29 and 1.48, respectively) and the risk of VLBW increased from 30 to 35 years of age (AOR 1.51). The change in risk of LBW with age was significantly different

TABLE 3

Adjusted odds ratios (95% confidence intervals) for maternal and neonatal outcomes for assisted reproductive technologies versus spontaneous conception at selected maternal ages.

Outcome	Age 25 y	Age 30 y	Age 35 y	Age 40 y	Age 45 y	Overall *P* value
Hypertensive disorders in pregnancy	1.42 (1.23–1.66) *P*<.0001	1.13 (1.02–1.24) *P*=.019	1.06 (0.96–1.18) *P*=.25	0.95 (0.80–1.14) *P*=.59	0.60 (0.28–1.31) *P*=.20	<.0001
Placental abruption	2.69 (1.90–3.81) *P*<.0001	1.83 (1.41–2.38) *P*<.0001	1.55 (1.17–2.05) *P*=.0020	1.71 (1.11–2.63) *P*=.015	1.74 (0.24–12.65) *P*=.58	<.0001
Placenta previa	5.65 (3.52–9.06) *P*<.0001	6.05 (4.71–7.76) *P*<.0001	4.11 (3.21–5.26) *P*<.0001	4.25 (2.83–6.39) *P*<.0001	2.60 (0.30–22.80) *P*=.39	<.0001
Cesarean section	1.50 (1.36–1.65) *P*<.0001	1.29 (1.22–1.36) *P*<.0001	1.18 (1.12–1.25) *P*<.0001	1.23 (1.12–1.34) *P*<.0001	1.22 (0.85–1.75) *P*=.28	<.0001
Preterm birth <37 wk	2.19 (1.94–2.47) *P*<.0001	1.58 (1.45–1.71) *P*<.0001	1.45 (1.33–1.59) *P*<.0001	1.23 (1.05–1.43) *P*=.0086	0.84 (0.44–1.61) *P*=.60	<.0001
Preterm birth <32 wk	3.20 (2.50–4.11) *P*<.0001	2.04 (1.70–2.46) *P*<.0001	1.68 (1.37–2.05) *P*<.0001	1.30 (0.94–1.81) *P*=.12	1.02 (0.27–3.81) *P*=.98	<.0001
Low birth weight < 2,500 g	2.35 (2.05–2.68) *P*<.0001	1.76 (1.60–1.94) *P*<.0001	1.44 (1.30–1.59) *P*<.0001	1.08 (0.91–1.28) *P*=.41	0.63 (0.30–1.34) *P*=.23	<.0001
Very low birth weight <1,500 g	3.44 (2.65–4.46) *P*<.0001	2.05 (1.68–2.50) *P*<.0001	1.67 (1.36–2.05) *P*<.0001	1.34 (0.94–1.90) *P*=.10	0.55 (0.12–2.52) *P*=.44	<.0001
Small for gestational age	1.43 (1.22–1.67) *P*<.0001	1.27 (1.14–1.41) *P*<.0001	1.10 (0.99–1.23) *P*=.067	0.83 (0.69–0.99) *P*=.044	0.23 (0.09–0.57) *P*=.0015	<.0001
Birth weight ≥4,500 g	0.88 (0.69–1.11) *P*=.28	0.97 (0.85–1.11) *P*=.66	0.76 (0.67–0.87) *P*<.0001	1.07 (0.86–1.34) *P*=.53	1.76 (0.73–4.23) *P*=.21	.0003
Perinatal mortality ≥28 wk	1.68 (1.02–2.77) *P*=.040	1.53 (1.12–2.10) *P*=.0083	1.00 (0.74–1.37) *P*=.98	1.00 (0.64–1.56) *P*=.99	1.00 (0.38–2.65) *P*=1.00	.049

Note: Adjusted odds ratios (adjusted for parity, year of birth, sex of offspring, and country) are based on piecewise logistic regression model. *P* values are presented for assisted reproductive technologies versus spontaneous conception.

Wennberg. Age and obstetrical outcome in ART. Fertil Steril 2016.

TABLE 4

Association between maternal and neonatal outcomes and maternal age in assisted reproductive technologies (ART) and spontaneous conception (SC): adjusted odds ratios [95% confidence intervals] for event by 5-y increase in maternal age.

	ART					SC					
Outcome	**< 30 y**	**30 to < 35 y**	**35 to < 40 y**	**≥40 y**	**Overall *P* value**	**< 30 y**	**30 to < 35 y**	**35 to < 40 y**	**≥40 y**	**Overall *P* value**	**Test for interaction between mode of conception and age for maternal age > 35 y: *P* value**
Hypertensive disorders in pregnancy	0.83 (0.69–0.99) *P*= .044 n = 608	1.02 (0.88–1.18) *P*= .77 n = 950	1.35 (1.12–1.62) *P*= .0014 n = 660	0.83 (0.40–1.72) *P*= .62 n = 64	.0007	1.04 (1.01–1.08) *P*= .021 n = 8,086	1.08 (1.00–1.17) *P*= .039 n = 2,969	1.51 (1.31–1.72) *P*< .0001 n = 1,058	1.32 (0.88–1.98) *P*= .19 n = 167	< .0001	.19
Placental abruption	0.67 (0.44–1.02) n = 91	1.06 (0.74–1.53) n = 134	1.41 (0.92–2.16) n = 114	0.53 (0.09–3.10) n = 9	.14	0.98 (0.87–1.10) *P*= .71 n = 732	1.26 (1.00–1.57) *P*= .046 n = 308	1.28 (0.88–1.85) *P*= .20 n = 131	0.52 (0.16–1.67) *P*= .27 n = 17	.0085	.93
Placenta previa	1.84 (1.08–3.12) *P*= .024 n = 102	1.28 (0.97–1.69) *P*= .081 n = 285	1.34 (0.98–1.83) *P*= .065 n = 232	0.27 (0.06–1.28) *P*= .099 n = 17	< .0001	1.72 (1.39–2.12) *P*< .0001 n = 262	1.88 (1.43–2.48) *P*< .0001 n = 218	1.30 (0.86–1.96) *P*= .22 n = 118	0.44 (0.08–2.52) *P*= .36 n = 10	< .0001	.92
Cesarean section	1.17 (1.04–1.31) *P*= .0079 n = 1,995	1.39 (1.29–1.50) *P*< .0001 n = 4,240	1.53 (1.39–1.68) *P*< .0001 n = 3,371	1.85 (1.32–2.58) *P*= .0003 n = 411	< .0001	1.36 (1.33–1.39) *P*< .0001 n = 23,244	1.51 (1.45–1.57) *P*< .0001 n = 12,458	1.47 (1.37–1.58) *P*< .0001 n = 5,008	1.86 (1.52–2.27) *P*< .0001 n = 857	< .0001	.80
Preterm birth <37 wk	0.70 (0.60–0.81) *P*< .0001 n = 948	1.06 (0.94–1.20) *P*= .32 n = 1,494	1.07 (0.92–1.25) *P*= .37 n = 983	0.73 (0.40–1.33) *P*= .31 n = 90	< .0001	0.97 (0.94–1.00) *P*= .090 n = 9,461	1.15 (1.08–1.23) *P*< .0001 n = 3,699	1.27 (1.13–1.44) *P*= .0001 n = 1,309	1.07 (0.74–1.52) *P*= .73 n = 198	< .0001	.043
Preterm birth <32 wk	0.62 (0.46–0.85) *P*= .0033 n = 197	1.04 (0.80–1.35) *P*= .76 n = 289	1.13 (0.81–1.57) *P*= .48 n = 195	0.94 (0.28–3.19) *P*= .93 n = 19	.027	0.98 (0.90–1.07) *P*= .62 n = 1,405	1.26 (1.07–1.49) *P*= .0059 n = 575	1.45 (1.10–1.92) *P*= .0079 n = 226	1.20 (0.58–2.51) *P*= .62 n = 40	< .0001	.36
Low birth weight <2,500 g	0.70 (0.59–0.83) *P*< .0001 n = 717	1.05 (0.92–1.20) *P*= .47 n = 1,105	1.10 (0.93–1.32) *P*= .27 n = 743	0.67 (0.33–1.36) *P*= .27 n = 63	.0002	0.93 (0.90–0.97) *P*= .0009 n = 6,531	1.29 (1.19–1.40) *P*< .0001 n = 2,554	1.48 (1.29–1.69) *P*< .0001 n = 1,006	1.14 (0.77–1.67) *P*= .51 n = 162	< .0001	.0021
Very low birth weight <1,500 g	0.57 (0.41–0.79) *P*= .0008 n = 171	1.23 (0.93–1.61) *P*= .14 n = 270	1.03 (0.73–1.47) *P*= .85 n = 179	0.70 (0.16–3.01) *P*= .64 n = 14	.019	0.95 (0.87–1.05) *P*= .33 n = 1,189	1.51 (1.27–1.80) *P*< .0001 n = 505	1.29 (0.97–1.72) *P*= .083 n = 218	1.72 (0.81–3.68) *P*= .16 n = 35	< .0001	.19
Small for gestational age	0.79 (0.65–0.97) *P*= .021 n = 538	1.24 (1.07–1.44) *P*= .0042 n = 970	1.01 (0.83–1.22) *P*= .95 n = 634	0.44 (0.18–1.08) *P*= .072 n = 42	.0057	0.89 (0.86–0.93) *P*< .0001 n = 7,352	1.43 (1.32–1.54) *P*< .0001 n = 2,741	1.34 (1.17–1.54) *P*< .0001 n = 1,014	1.61 (1.11–2.34) *P*= .012 n = 178	< .0001	< .0001
Birth weight ≥4,500 g	1.29 (0.97–1.72) n = 280	0.83 (0.68–1.00) n = 536	1.15 (0.90–1.48) n = 363	1.19 (0.52–2.72) n = 46	.25	1.17 (1.12–1.22) *P*< .0001 n = 5,184	1.05 (0.97–1.14) *P*= .25 n = 2,713	0.82 (0.71–0.95) *P*= .0094 n = 903	0.73 (0.45–1.17) *P*= .19 n = 109	< .0001	.0078
Perinatal mortality ≥28 wk	0.86 (0.46–1.58) n = 55	1.05 (0.68–1.63) n = 100	0.95 (0.59–1.53) n = 67	0.95 (0.59–1.53) n = 7	.96	0.94 (0.83–1.07) *P*= .35 n = 638	1.60 (1.28–2.01) *P*< .0001 n = 302	0.95 (0.70–1.29) *P*= .74 n = 119	0.95 (0.70–1.29) *P*= .74 n = 14	< .0001	.99

Note: Adjusted odds ratios (adjusted for parity, year of birth, sex of offspring, and country) are based on piecewise logistic regression model.

Wennberg. Age and obstetrical outcome in ART. Fertil Steril 2016.

between ART and SC singletons in women of maternal age >35 years of age (P=.0021, test for interaction), with an increased risk for SC pregnancies at maternal age >35 years but not for ART pregnancies. The change in risk of VLBW with age did not differ between ART and SC singletons at maternal age >35 years (P=.19, test for interaction; Tables 3 and 4; Supplemental Figs. 8 and 9).

The risk of SGA was significantly higher in ART than in SC singletons at 25 and 30 years (AORs 1.43 and 1.27, respectively), and significantly lower at 40 and 45 years (AORs 0.83 and 0.23, respectively). The risks of SGA in ART and SC singletons changed by age. In ART there was a decrease before 30 years of age and an increase from 30 to 35 (AOR 1.24). In SC singletons, there was a decrease before 30 years and thereafter an increase (AORs 1.34–1.61). The change in risk of SGA with age differed between ART and SC singletons at maternal age >35 years (P<.0001, test for interaction), with an increased risk seen for SC pregnancies at maternal age >35 years, but not for ART pregnancies (Tables 3 and 4; Supplemental Fig. 10).

The risk of macrosomia was significantly lower in ART than in SC singletons among women at 35 years of age (AOR 0.76). The risk of macrosomia in ART did not change with maternal age. In SC singletons, the risk was higher before 30 years (AOR 1.17) and lower at 35–40 years of age. The change in risk of macrosomia with age differed between ART and SC singletons at maternal age >35 years (P=.0078, test for interaction), with the risk of macrosomia decreasing with maternal age in SC pregnancies (Tables 3 and 4; Supplemental Fig. 11).

The risk of perinatal mortality was significantly higher at 25 and 30 years in ART (AORs 1.68 and 1.53, respectively) than in SC. Perinatal mortality in ART singletons did not increase by maternal age, whereas it increased with age from 30 to 35 years in SC pregnancies (AOR 1.60). The change in risk of perinatal mortality with age did not differ between ART and SC pregnancies at maternal age >35 years (P<.99, test for interaction; Tables 3 and 4; Supplemental Fig. 12).

In general, the unadjusted analyses showed similar results to the adjusted analyses (Supplemental Tables 1 and 2).

DISCUSSION

In this large population-based Nordic cohort study, we evaluated maternal and neonatal risks associated with maternal age in births resulting from ART as opposed to SC.

The risk of placental abruption, placenta previa, cesarean delivery, PTB, very PTB, and VLBW was significantly higher in ART pregnancies than in SC pregnancies for most maternal ages. In both ART and SC pregnancies, the risk of HDP and cesarean delivery increased in women of >35 years of age. The change in risk of adverse maternal outcomes with age did not differ between ART and SC pregnancies in women >35 years of age. In ART singletons, the risk of adverse neonatal outcomes did not increase in women >35 years of age, whereas the risk of PTB, very PTB, LBW, and SGA increased in SC singletons. The change in risk of PTB, LBW, and SGA with age differed between ART and SC singletons in women >35 years of age.

The main strengths of the present study are the large number of ART pregnancies in the Conartas cohort, the large group of control subjects, the population-based design, and the high data quality in the Nordic health registries (11–14). Weaknesses include the limited number of mothers of very advanced reproductive age (>45 years of age), and potential unmeasured confounders. More than 1,000 women >40 years of age were included in the ART group, but the number of events for many outcomes was few, thus reducing the statistical power in this age category. It was only possible to adjust for parity, year of birth, offspring sex, and country. Thus, there may be residual confounding due to factors such as maternal body mass index, smoking, and cause of infertility that are not included in the registries. Smoking and body mass index have previously been shown to be associated with PTB and SGA in ART pregnancies (15). Smoking has also been found to be associated with placental abruption in both ART (15) and in SC (16) pregnancies. However, in national studies in Sweden and Norway (17, 18) smoking was less frequent among ART patients, indicating that smoking can not explain the higher rate of abruption in ART pregnancies. In earlier national studies, vanishing twins have been found to be associated with a poorer neonatal outcome (15, 19), explaining a part of the poorer outcome for ART singletons. We could not adjust for vanishing twin or selective reduction. A large part of the singletons in the present study were born during a time period where single-embryo transfer was being performed (in Sweden ~75% since the early 2000s), so the contribution of vanishing twins to the general poorer outcome in ART is small. Selective reduction is an extremely uncommon procedure in the Nordic countries. Because the impact of age seemed to be more pronounced in women who conceived spontaneously it is unlikely that vanishing twins and selective reduction contributed to the age-related differences in this study.

Furthermore, a major limitation was that it was not possible to adjust for socioeconomic variables. Up to 40 years of age, ART is free of charge or heavily subsidized in the public health care system in the Nordic countries. ART treatment is generally not funded by the state when the woman is >40 years of age. ART mothers >40 years of age may constitute a socioeconomic group that is economically stronger, better educated, and healthier than many older SC mothers, all of which may contribute to the absence of excess risk in older ART mothers. In all of the Nordic countries, prenatal care programs are free of charge and provided by the public health care systems. Reporting births to each country's national registry is a routine procedure and not dependent on method of conception. During most of the study period, women with ART pregnancies have followed the same prenatal care programs as the general population. However, older women with ART pregnancies may be more observant of their state of health and seek medical attention more often than other women, which could result in earlier or increased detection of complications.

A control group from the general population is not an ideal solution to separate patient characteristics from ART procedure factors that may be associated with poorer

obstetrical outcomes in ART, because the two populations are different. Using a subfertile control group or a sibling design would be more appropriate. Unfortunately, large and complete cohorts of this kind do not exist. A few studies using sibling design have indicated that both patient characteristics and ART procedures are associated with poorer obstetrical outcomes (20, 21). The present study question would, however, not be possible to investigate in such a cohort using sibling design, even if large, mainly owing to too few siblings. Furthermore, because age-related risks increased more in SC than in ART, we do not think that the difference is explained by infertility or subfertility factors.

This study did not include pregnancies achieved with the use of oocyte donation (OD). Such pregnancies are associated with more complications than IVF with own oocytes and can also be assumed to be more common among older mothers (22–24). If there are pregnancies as a result of reproductive tourism, i.e., OD treatments in other countries, they would incorrectly be assigned as SC pregnancies, contributing to an age-related risk increase in the SC group. The contribution of this group of oocyte recipients to the results of the study is, however, likely to be negligible, considering the large number of SC pregnancies included.

Only fresh cycles were included for several reasons. Earlier studies have demonstrated different neonatal outcomes for children born after frozen and fresh embryo transfer. The risk of PTB and LBW seem to be lower, but the rate of LGA neonates seems to be higher in singletons born after frozen embryo transfer than after fresh transfer (25–27). Moreover, in the present study it was only possible to take into account the mother's age at the time of embryo transfer. For fresh cycles, the mother's age at embryo transfer is the same as the age of the oocytes, whereas for frozen-thawed cycles a difference of up to 5 years may occur because legislation in the Nordic countries allows embryos to be cryopreserved for that length of time. This discrepancy might complicate the interpretation of age-related risks.

It is well known that advanced maternal age increases the risk of adverse neonatal and maternal outcomes (2–5). Furthermore, the risk of maternal complications such as HDP, placenta previa, and caesarean delivery, as well as the risk of poor neonatal outcome, is higher among ART pregnancies (6–8). Few studies have, however, examined the age-related risks associated specifically with ART conceptions. A large American study using data from the Society for Assisted Reproductive Technology Clinic Online Reporting System showed decreasing rates of PTB with increasing maternal age in births resulting from ART (28). Although not correlated with a control group, that finding is in line with our results and implies that maternal age is not as strong a risk factor in ART pregnancies as in SC pregnancies.

Our study included several outcomes and therefore multiple statistical analyses. The overall test partially corrected for this. We chose not to further correct for multiple analyses, which would have reduced the number of randomly inflated (i.e., false positive) associations, because we thought it was more important not to increase the number of randomly deflated (i.e., false negative) associations, which could result in missing important side-effects of ART (29).

There may be several reasons for the finding that although risks of adverse neonatal outcome increase with age in SC pregnancies, this is not the case, or it is so to a lesser extent, in women in the ART group. The indications for ART may be different in older and younger women. ART in older women may more often be the result of age-related infertility in otherwise healthy women, whereas younger women are more likely to have other underlying disorders that can contribute to increased risks in pregnancy. Women who conceive through ART at an advanced age may also, for medical and socioeconomic reasons, represent a healthier group than the general population.

CONCLUSION

Although the risk of adverse maternal and neonatal outcomes was significantly higher in ART than in SC pregnancies for most maternal ages, the increase in risk with age for adverse neonatal outcomes was more pronounced in SC. Similar age-related changes were observed for maternal outcomes in both ART and SC. The results are important for the large group of women undergoing ART at an advanced age and for clinicians treating them.

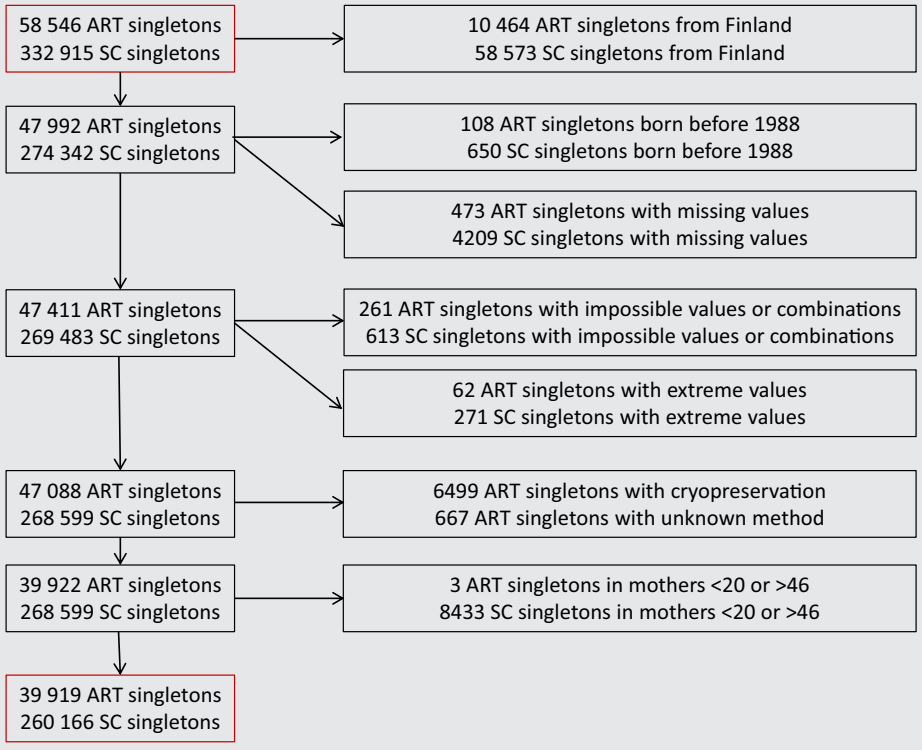
Acknowledgments: The authors thank Nils-Gunnar Pehrsson and Henrik Imberg, Statistical Consulting Group, Gothenburg. The authors also acknowledge the work carried out at all the Nordic fertility clinics that recorded data on ART procedures through the years.

REFERENCES

1. National Institute for Health and Welfare. Nordic perinatal statistics 2014. Helsinki, Finland. Available at: https://www.thl.fi/en/web/thlfi-en/statistics/statistics-by-topic/sexual-and-reproductive-health/parturients-deliveries-and-births/nordic-perinatal-statistics. Accessed May 14, 2016.
2. Carolan M. Maternal age ≥ 45 years and maternal and perinatal outcomes: a review of the evidence. Midwifery 2013;29:479–89.
3. Jacobsson B, Ladfors L, Milsom I. Advanced maternal age and adverse perinatal outcome. Obstet Gynecol 2004;104:727–33.
4. Paulson RJ, Boostanfar R, Saadat P, Mor E, Tourgeman DE, Slater CC, et al. Pregnancy in the sixth decade of life: obstetric outcomes in women of advanced reproductive age. JAMA 2002;288:2320–3.
5. Haavaldsen C, Sarfraz AA, Samuelsen SO, Eskild A. The impact of maternal age on fetal death: does length of gestation matter? Am J Obstet Gynecol 2010;203:554.e1–8.
6. Helmerhorst FM, Perquin DA, Donker D, Keirse MJ. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. BMJ 2004;328:261–6.
7. Jackson RA, Gibson KA, Wu YW, Croughan MS. Perinatal outcomes in singletons following in vitro fertilization: a meta-analysis. Obstet Gynecol 2004;103:551–63.
8. Mc Donald SD, Mulla S, Murphy KE, Beyene J, Ohlsson A. Preterm birth and low birth weight among in vitro fertilization singletons: a systematic review and meta-analyses. Eur J Obstet Gynecol Reprod Biol 2009;146:138–48.
9. Henningsen AK, Romundstad LB, Gissler M, Nygren KG, Lidegaard O, Skjaerven R, et al. Infant and maternal health monitoring using a combined Nordic database on ART and safety. Acta Obstet Gynecol Scand 2011;90:683–91.
10. Marsal K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Paediatr 1996;85:843–8.
11. Cnattingius S, Ericson A, Gunnarskog J, Kallen B. A quality study of a medical birth registry. Scand J Soc Med 1990;18:143–8.

12. Gissler M, Louhiala P, Hemminki E. Nordic medical birth registers in epidemiological research. Eur J Epidemiol 1997;13:169–75.
13. Langhoff-Roos J, Krebs L, Klungsoyr K, Bjarnadottir RI, Kallen K, Tapper AM, et al. The Nordic medical birth registers—a potential goldmine for clinical research. Acta Obstet Gynecol Scand 2014;93:132–7.
14. National Board of Health and Welfare. The Swedish medical birth registry—a summary of content and quality. Available at: http://www.socialstyrelsen.se/publikationer//2003/2003-112-3; 2003. Accessed May 14, 2016.
15. Sazonova A, Källen K, Thurin-Kjellberg A, Wennerholm UB, Bergh C. Factors affecting obstetric outcome of singletons born after IVF. Hum Reprod 2011;26:2878–86.
16. Oyelese Y, Ananth CV. Placental abruption. Obstet Gynecol 2006;108:1005–16.
17. Sazonova A, Källen K, Thurin-Kjellberg A, Wennerholm UB, Bergh C. Obstetric outcome after in vitro fertilization with single or double embryo transfer. Hum Reprod 2011;26:442–50.
18. Tandberg A, Klungsøyr K, Romundstad LB, Skjærven R. Pre-eclampsia and assisted reproductive technologies: consequences of advanced maternal age, interbirth intervals, new partner and smoking habits. BJOG 2015;122:915–22.
19. Pinborg A, Wennerholm UB, Romundstad LB, Loft A, Aittomaki K, Söderström-Anttila V, et al. Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis. Hum Reprod Update 2013;19:87–104.
20. Romundstad LB, Romundstad PR, Sunde A, von Düring V, Skjaerven R, Gunnell D, et al. Effects of technology or maternal factors on perinatal outcome after assisted fertilisation: a population-based cohort study. Lancet 2008;372:737–43.
21. Henningsen AK, Pinborg A, Lidegaard Ø, Vestergaard C, Forman JL, Andersen AN. Perinatal outcome of singleton siblings born after assisted reproductive technology and spontaneous conception: Danish national sibling-cohort study. Fertil Steril 2011;95:959–63.
22. Gibbons WE, Cedars M, Ness RB, Society for Assisted Reproductive Technologies Writing Group. Toward understanding obstetrical outcome in advanced assisted reproduction: varying sperm, oocyte, and uterine source and diagnosis. Fertil Steril 2011;95:1645–9.e1.
23. Malchau SS, Loft A, Larsen EC, Aaris Henningsen AK, Rasmussen S, Andersen AN, et al. Perinatal outcomes in 375 children born after oocyte donation: a Danish national cohort study. Fertil Steril 2013;99:1637–43.
24. van der Hoorn ML, Lashley EE, Bianchi DW, Claas FH, Schonkeren CM, Scherjon SA. Clinical and immunologic aspects of egg donation pregnancies: a systematic review. Hum Reprod Update 2010;16:704–12.
25. Pelkonen S, Koivunen R, Gissler M, Nuojua-Huttunen S, Suikkari AM, Hyden-Granskog C, et al. Perinatal outcome of children born after frozen and fresh embryo transfer: the Finnish cohort study 1995–2006. Hum Reprod 2010;25:914–23.
26. Pinborg A, Henningsen AA, Loft A, Malchau SS, Forman J, Andersen AN. Large baby syndrome in singletons born after frozen embryo transfer (FET): is it due to maternal factors or the cryotechnique? Hum Reprod 2014;29:618–27.
27. Wennerholm UB, Henningsen AK, Romundstad LB, Bergh C, Pinborg A, Skjaerven R, et al. Perinatal outcomes of children born after frozen-thawed embryo transfer: a Nordic cohort study from the Conartas group. Hum Reprod 2013;28:2545–53.
28. Xiong X, Dickey RP, Pridjian G, Buekens P. Maternal age and preterm births in singleton and twin pregnancies conceived by in vitro fertilisation in the United States. Paediatr Perinat Epidemiol 2015;29:22–30.
29. Rothman KJ. No adjustments are needed for multiple comparisons. Epidemiology 1990;1:43–6.

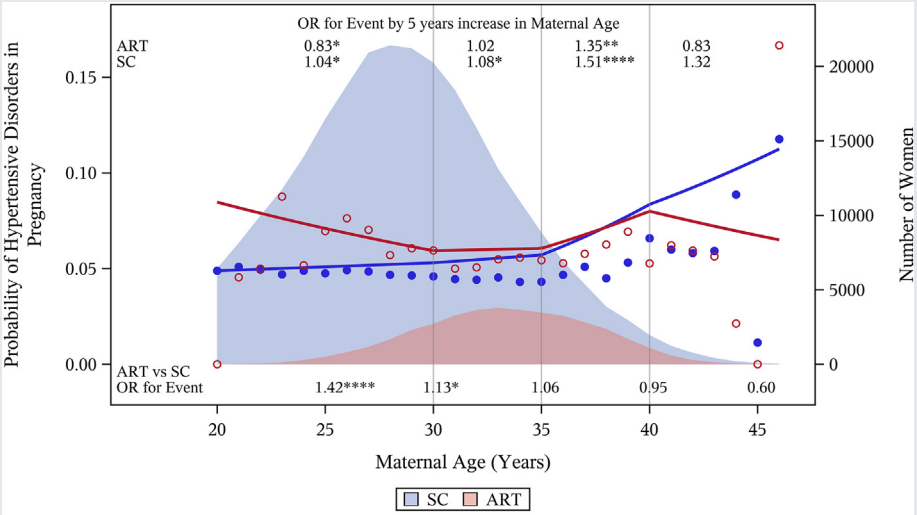
SUPPLEMENTAL FIGURE 1



Flowchart of the study population.

Wennberg. Age and obstetrical outcome in ART. Fertil Steril 2016.

SUPPLEMENTAL FIGURE 2

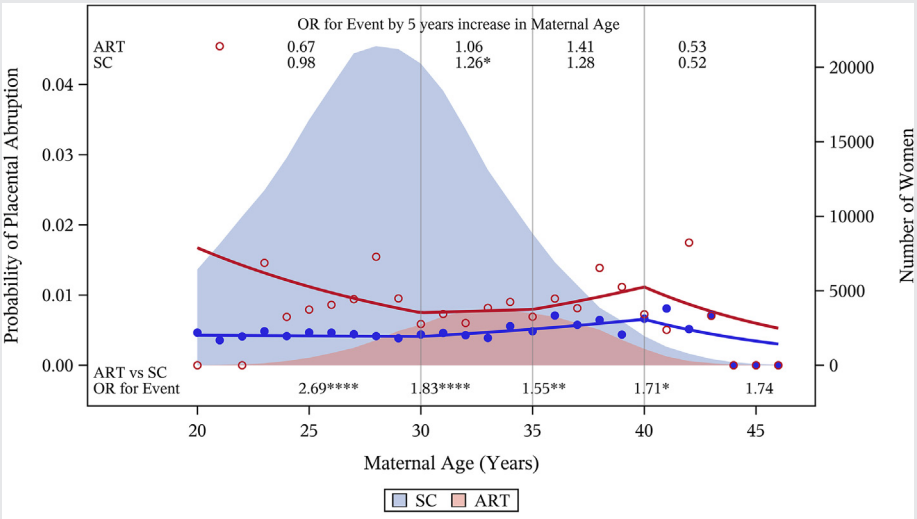


Dots represent raw data, the shaded region in the background is the age distribution in the cohort.
Lines are adjusted probabilities of outcome as function of maternal age, evaluated at median parity and year of birth and with weights on offspring sex and country according to the distribution in the cohort.
Test for interaction between mode of conception and age in advanced maternal age >35 years: P=.19
All analyses are adjusted for parity, year of birth, offspring sex and country.
* P<.05, ** P<.01,*** P<.001, **** P<.0001

Hypertensive disorders in pregnancy for assisted reproductive technology (ART) and spontaneous conception (SC) by maternal age. OR = odds ratio.

Wennberg. Age and obstetrical outcome in ART. Fertil Steril 2016.

SUPPLEMENTAL FIGURE 3

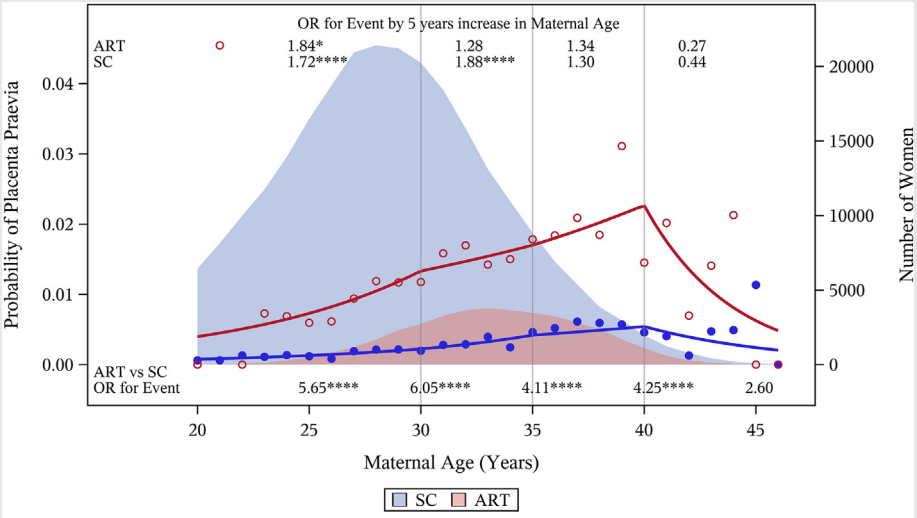


Dots represent raw data, the shaded region in the background is the age distribution in the cohort.
Lines are adjusted probabilities of outcome as function of maternal age, evaluated at median parity and year of birth and with weights on offspring sex and country according to the distribution in the cohort.
Test for interaction between mode of conception and age in advanced maternal age >35 years: P=.93
All analyses are adjusted for parity, year of birth, offspring sex and country.
* P<.05, ** P<.01, *** P<.001, **** P<.0001

Placental abruption for assisted reproductive technology (ART) and spontaneous conception (SC) by maternal age. OR = odds ratio.

Wennberg. Age and obstetrical outcome in ART. Fertil Steril 2016.

SUPPLEMENTAL FIGURE 4

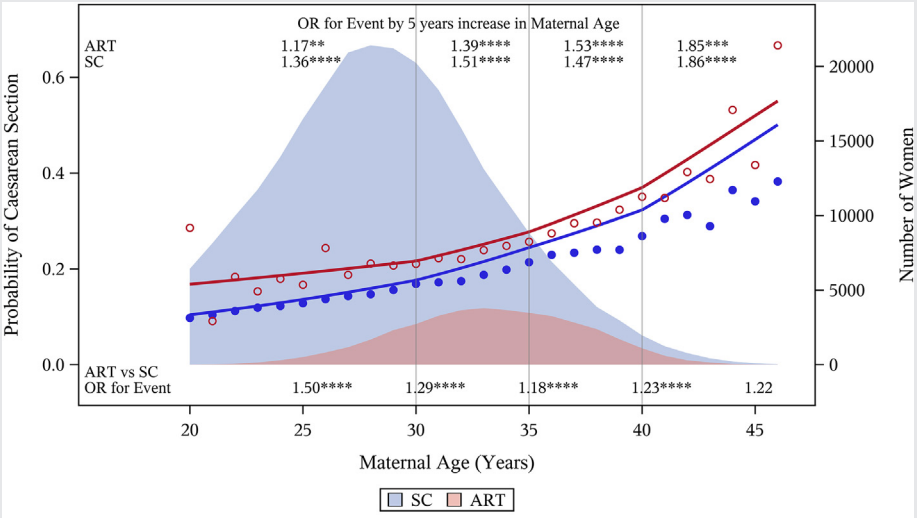


Dots represent raw data, the shaded region in the background is the age distribution in the cohort.
Lines are adjusted probabilities of outcome as function of maternal age, evaluated at median parity and year of birth and with weights on offspring sex and country according to the distribution in the cohort.
Test for interaction between mode of conception and age in advanced maternal age >35 years: P=.92
All analyses are adjusted for parity, year of birth, offspring sex and country.
* P<.05, ** P<.01, *** P<.001, **** P<.0001

Placenta previa for assisted reproductive technology (ART) and spontaneous conception (SC) by maternal age. OR = odds ratio.

Wennberg. Age and obstetrical outcome in ART. Fertil Steril 2016.

SUPPLEMENTAL FIGURE 5

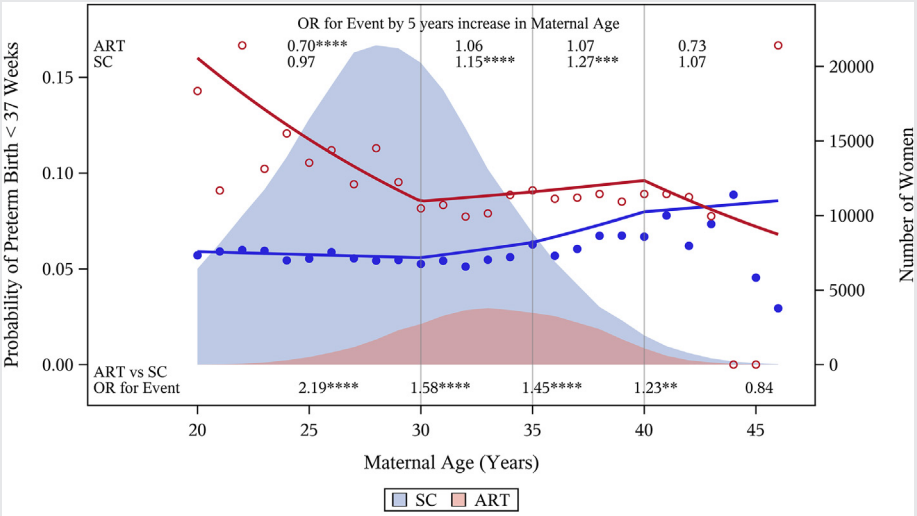


Dots represent raw data, the shaded region in the background is the age distribution in the cohort.
Lines are adjusted probabilities of outcome as function of maternal age, evaluated at median parity and year of birth and with weights on offspring sex and country according to the distribution in the cohort.
Test for interaction between mode of conception and age in advanced maternal age >35 years: *P*=.80
All analyses are adjusted for parity, year of birth, offspring sex and country.
* *P*<.05, ** *P*<.01, *** *P*<.001, **** *P*<.0001

Cesarean section for assisted reproductive technology (ART) and spontaneous conception (SC) by maternal age. OR = odds ratio.

Wennberg. Age and obstetrical outcome in ART. Fertil Steril 2016.

SUPPLEMENTAL FIGURE 6

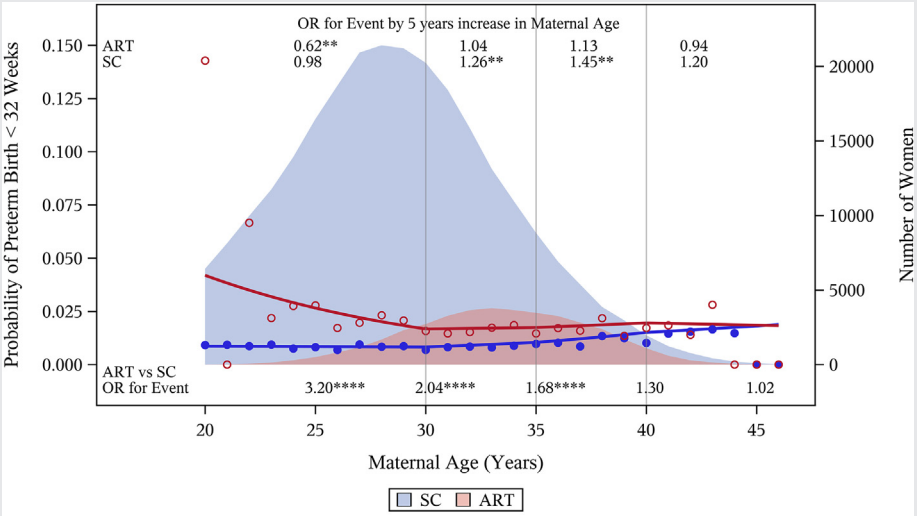


Dots represent raw data, the shaded region in the background is the age distribution in the cohort.
Lines are adjusted probabilities of outcome as function of maternal age, evaluated at median parity and year of birth and with weights on offspring sex and country according to the distribution in the cohort.
Test for interaction between mode of conception and age in advanced maternal age >35 years: *P*=.043
All analyses are adjusted for parity, year of birth, offspring sex and country.
* *P*<.05, ** *P*<.01, *** *P*<.001, **** *P*<.0001

Preterm birth <37 weeks for assisted reproductive technology (ART) and spontaneous conception (SC) by maternal age. OR = odds ratio.

Wennberg. Age and obstetrical outcome in ART. Fertil Steril 2016.

SUPPLEMENTAL FIGURE 7

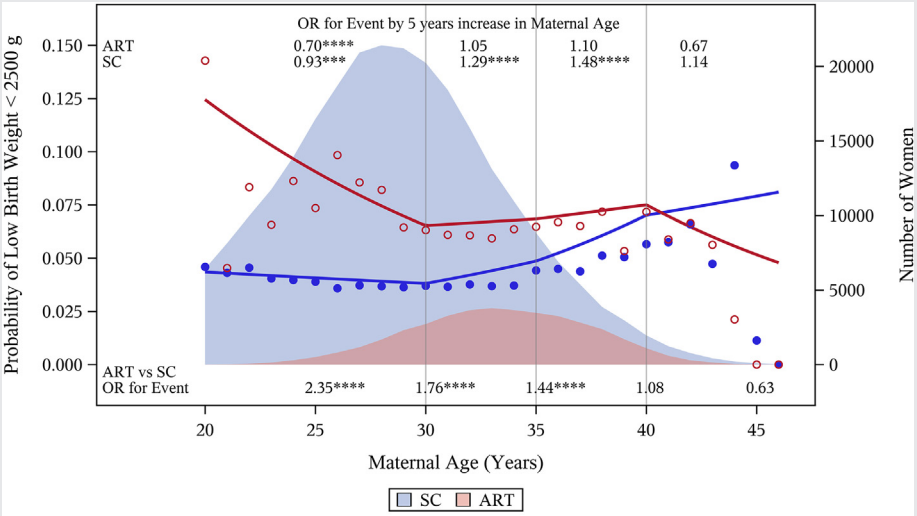


Dots represent raw data, the shaded region in the background is the age distribution in the cohort.
Lines are adjusted probabilities of outcome as function of maternal age, evaluated at median parity and year of birth and with weights on offspring sex and country according to the distribution in the cohort.
Test for interaction between mode of conception and age in advanced maternal age >35 years: P=.36
All analyses are adjusted for parity, year of birth, offspring sex and country.
* P<.05, ** P<.01, *** P<.001, **** P<.0001

Preterm birth <32 weeks for assisted reproductive technology (ART) and spontaneous conception (SC) by maternal age. OR = odds ratio.

Wennberg. Age and obstetrical outcome in ART. Fertil Steril 2016.

SUPPLEMENTAL FIGURE 8

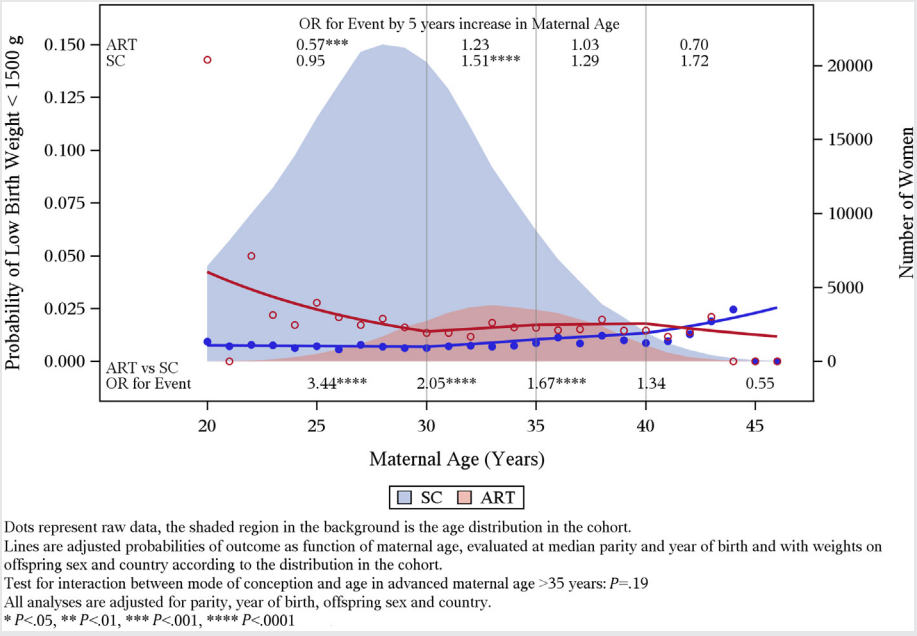


Dots represent raw data, the shaded region in the background is the age distribution in the cohort.
Lines are adjusted probabilities of outcome as function of maternal age, evaluated at median parity and year of birth and with weights on offspring sex and country according to the distribution in the cohort.
Test for interaction between mode of conception and age in advanced maternal age >35 years: *P*=.0021
All analyses are adjusted for parity, year of birth, offspring sex and country.
* *P*<.05, ** *P*<.01, *** *P*<.001, **** *P*<.0001

Low birth weight <2,500 g for assisted reproductive technology (ART) and spontaneous conception (SC) by maternal age. OR = odds ratio.

Wennberg. Age and obstetrical outcome in ART. Fertil Steril 2016.

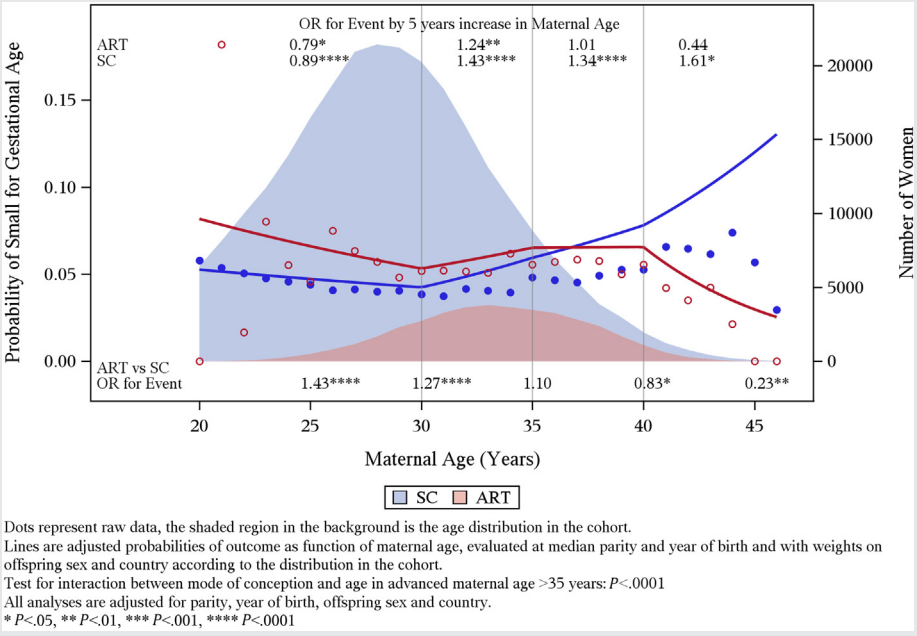
SUPPLEMENTAL FIGURE 9



Very low birth weight <1,500 g for assisted reproductive technology (ART) and spontaneous conception (SC) by maternal age. OR = odds ratio.

Wennberg. Age and obstetrical outcome in ART. Fertil Steril 2016.

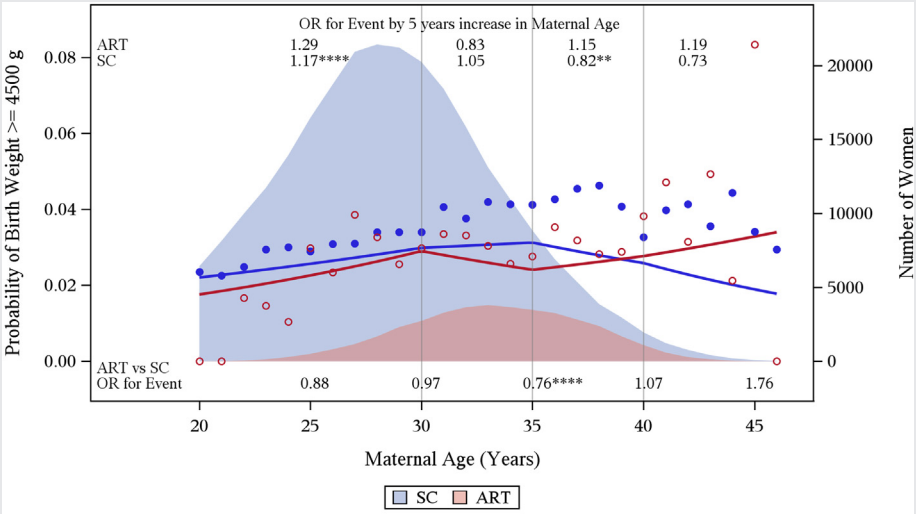
SUPPLEMENTAL FIGURE 10



Small for gestational age for assisted reproductive technology (ART) and spontaneous conception (SC) by maternal age. OR = odds ratio.

Wennberg. Age and obstetrical outcome in ART. Fertil Steril 2016.

SUPPLEMENTAL FIGURE 11

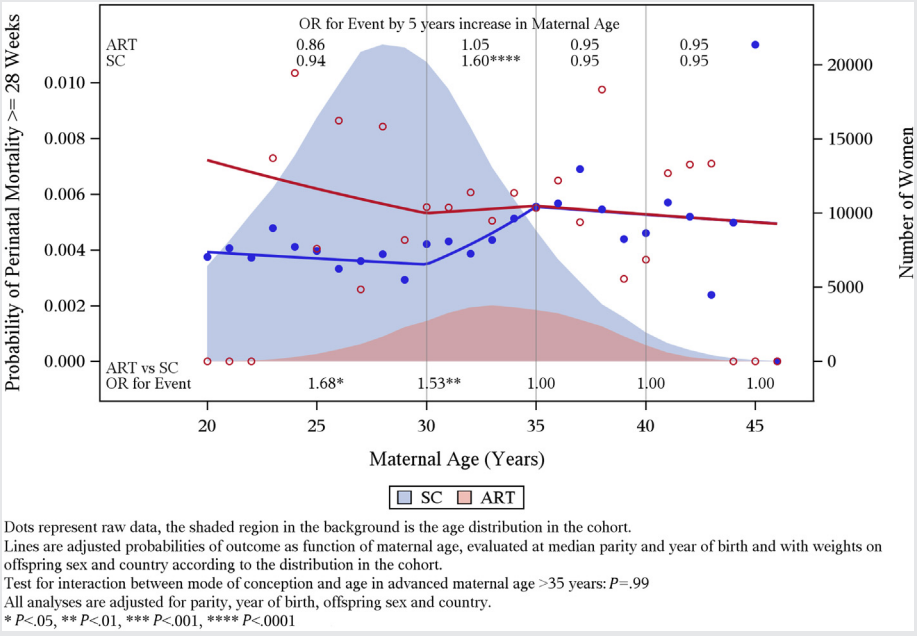


Dots represent raw data, the shaded region in the background is the age distribution in the cohort.
Lines are adjusted probabilities of outcome as function of maternal age, evaluated at median parity and year of birth and with weights on offspring sex and country according to the distribution in the cohort.
Test for interaction between mode of conception and age in advanced maternal age >35 years: *P*=.0078
All analyses are adjusted for parity, year of birth, offspring sex and country.
* *P*<.05, ** *P*<.01, *** *P*<.001, **** *P*<.0001

Birth weight ≥4,500 g for assisted reproductive technology (ART) and spontaneous conception (SC) by maternal age. OR = odds ratio.

Wennberg. Age and obstetrical outcome in ART. Fertil Steril 2016.

SUPPLEMENTAL FIGURE 12



Dots represent raw data, the shaded region in the background is the age distribution in the cohort.
Lines are adjusted probabilities of outcome as function of maternal age, evaluated at median parity and year of birth and with weights on offspring sex and country according to the distribution in the cohort.
Test for interaction between mode of conception and age in advanced maternal age >35 years: P=.99
All analyses are adjusted for parity, year of birth, offspring sex and country.
* P<.05, ** P<.01, *** P<.001, **** P<.0001

Perinatal mortality ≥28 weeks for assisted reproductive technology (ART) and spontaneous conception (SC) by maternal age OR = odds ratio.

Wennberg. Age and obstetrical outcome in ART. Fertil Steril 2016.

SUPPLEMENTAL TABLE 1

Unadjusted odds ratios for maternal and neonatal outcomes for assisted reproductive technologies (ART) versus spontaneous conception at selected maternal ages.

Outcome	25 y	30 y	35 y	40 y	45 y	Overall *P* value
Hypertensive disorders in pregnancy	1.48 (1.27–1.71) *P*<.0001	1.23 (1.11–1.35) *P*<.0001	1.26 (1.13–1.40) *P*<.0001	1.12 (0.94–1.33) *P*=.20	0.71 (0.33–1.52) *P*=.38	<.0001
Placental abruption	2.62 (1.86–3.70) *P*<.0001	1.82 (1.41–2.36) *P*<.0001	1.55 (1.18–2.04) *P*=.0017	1.69 (1.10–2.60) *P*=.017	1.66 (0.22–12.29) *P*=.62	<.0001
Placenta previa	5.64 (3.52–9.04) *P*<.0001	5.94 (4.64–7.62) *P*<.0001	3.94 (3.10–5.00) *P*<.0001	4.04 (2.71–6.01) *P*<.0001	2.46 (0.28–21.61) *P*=.42	<.0001
Cesarean section	1.64 (1.49–1.80) *P*<.0001	1.38 (1.31–1.46) *P*<.0001	1.32 (1.25–1.40) *P*<.0001	1.42 (1.30–1.55) *P*<.0001	1.56 (1.10–2.23) *P*=.013	<.0001
Preterm birth <37 wk	2.19 (1.94–2.47) *P*<.0001	1.62 (1.49–1.76) *P*<.0001	1.56 (1.42–1.70) *P*<.0001	1.31 (1.13–1.52) *P*=.0005	0.90 (0.47–1.72) *P*=.75	<.0001
Preterm birth <32 wk	3.13 (2.45–4.01) *P*<.0001	2.11 (1.75–2.54) *P*<.0001	1.82 (1.49–2.22) *P*<.0001	1.39 (1.00–1.93) *P*=.052	1.07 (0.28–4.01) *P*=.92	<.0001
Low birth weight <2,500 g	2.35 (2.06–2.69) *P*<.0001	1.85 (1.68–2.03) *P*<.0001	1.60 (1.45–1.77) *P*<.0001	1.20 (1.01–1.42) *P*=.035	0.71 (0.34–1.50) *P*=.37	<.0001
Very low birth weight <1,500 g	3.34 (2.58–4.33) *P*<.0001	2.14 (1.76–2.61) *P*<.0001	1.85 (1.51–2.27) *P*<.0001	1.46 (1.03–2.07) *P*=.033	0.58 (0.13–2.72) *P*=.49	<.0001
Small for gestational age	1.45 (1.24–1.69) *P*<.0001	1.38 (1.24–1.53) *P*<.0001	1.33 (1.20–1.48) *P*<.0001	1.00 (0.83–1.19) *P*=.96	0.27 (0.11–0.68) *P*=.0058	<.0001
Birth weight ≥4,500 g	0.84 (0.66–1.06) *P*=.14	0.89 (0.78–1.01) *P*=.079	0.64 (0.56–0.73) *P*<.0001	0.85 (0.69–1.06) *P*=.16	1.23 (0.52–2.93) *P*=.63	<.0001
Perinatal mortality ≥28 wk	1.63 (0.99–2.67) *P*=.054	1.54 (1.12–2.11) *P*=.0071	1.03 (0.76–1.40) *P*=.84	1.00 (0.64–1.57) *P*=.98	0.98 (0.37–2.61) *P*=.96	.043

Note: Odds ratios are based on piecewise logistic regression. *P* values are presented for assisted reproductive technologies versus spontaneous conception.

Wennberg. Age and obstetrical outcome in ART. Fertil Steril 2016.

SUPPLEMENTAL TABLE 2

Association between maternal and neonatal outcomes and maternal age in assisted reproductive technologies and spontaneous conception: unadjusted odds ratios for event by 5-y increase in maternal age.

	ART					SC					
Outcome	**< 30 y**	**30 to < 35 y**	**35 to < 40 y**	**≥40 y**	**Overall *P* value**	**< 30 y**	**30 to < 35 y**	**35 to < 40 y**	**≥40 y**	**Overall *P* value**	**Test for interaction between mode of conception and age for maternal age > 35 y: *P* value**
Hypertensive disorders in pregnancy	0.79 (0.66–0.96) *P*=.015 n = 608	0.95 (0.82–1.10) *P*=.52 n = 950	1.23 (1.02–1.47) *P*=.029 n = 660	0.71 (0.34–1.46) *P*=.35 n = 64	.011	0.96 (0.92–0.99) *P*=.012 n = 8,086	0.93 (0.86–1.00) *P*=.046 n = 2,969	1.38 (1.21–1.58) *P*<.0001 n = 1,058	1.12 (0.76–1.64) *P*=.58 n = 167	<.0001	.16
Placental abruption	0.67 (0.44–1.03) n = 91	1.07 (0.74–1.54) n = 134	1.40 (0.91–2.14) n = 114	0.53 (0.09–3.12) n = 9	.16	0.97 (0.86–1.09) *P*=.62 n = 732	1.26 (1.01–1.57) *P*=.043 n = 308	1.28 (0.88–1.86) *P*=.19 n = 131	0.53 (0.17–1.71) *P*=.29 n = 17	.0045	.95
Placenta previa	1.84 (1.09–3.13) *P*=.023 n = 102	1.29 (0.98–1.71) *P*=.070 n = 285	1.36 (1.00–1.85) *P*=.053 n = 232	0.28 (0.06–1.31) *P*=.11 n = 17	<.0001	1.75 (1.42–2.15) *P*<.0001 n = 262	1.95 (1.49–2.56) *P*<.0001 n = 218	1.32 (0.88–2.00) *P*=.18 n = 118	0.46 (0.08–2.63) *P*=.38 n = 10	<.0001	.91
Cesarean section	1.12 (1.00–1.26) *P*=.053 n = 1,995	1.29 (1.19–1.39) *P*<.0001 n = 4,240	1.47 (1.34–1.61) *P*<.0001 n = 3,371	1.74 (1.25–2.42) *P*=.0010 n = 411	<.0001	1.32 (1.29–1.35) *P*<.0001 n = 23,244	1.35 (1.30–1.40) *P*<.0001 n = 12,458	1.37 (1.28–1.47) *P*<.0001 n = 5,008	1.58 (1.30–1.92) *P*<.0001 n = 857	<.0001	.30
Preterm birth <37 wk	0.69 (0.60–0.81) *P*<.0001 n = 948	1.04 (0.92–1.17) *P*=.51 n = 1,494	1.04 (0.89–1.21) *P*=.65 n = 983	0.69 (0.37–1.25) *P*=.22 n = 90	<.0001	0.94 (0.91–0.97) *P*=.0001 n = 9,461	1.09 (1.01–1.16) *P*=.017 n = 3,699	1.23 (1.09–1.39) *P*=.0008 n = 1,309	1.00 (0.70–1.42) *P*=.99 n = 198	<.0001	.041
Preterm birth <32 wk	0.63 (0.46–0.85) *P*=.0032 n = 197	1.02 (0.79–1.32) *P*=.90 n = 289	1.07 (0.77–1.48) *P*=.70 n = 195	0.86 (0.25–2.94) *P*=.81 n = 19	.020	0.93 (0.85–1.01) *P*=.090 n = 1,405	1.18 (1.00–1.39) *P*=.049 n = 575	1.40 (1.06–1.85) *P*=.017 n = 226	1.11 (0.54–2.30) *P*=.77 n = 40	<.0001	.31
Low birth weight <2,500 g	0.70 (0.59–0.82) *P*<.0001 n = 717	1.01 (0.88–1.16) *P*=.88 n = 1,105	1.05 (0.88–1.25) *P*=.58 n = 743	0.61 (0.30–1.24) *P*=.17 n = 63	<.0001	0.89 (0.85–0.92) *P*<.0001 n = 6,531	1.17 (1.08–1.26) *P*=.0001 n = 2,554	1.40 (1.22–1.61) *P*<.0001 n = 1,006	1.03 (0.70–1.51) *P*=.87 n = 162	<.0001	.0022
Very low birth weight <1,500 g	0.57 (0.41–0.79) *P*=.0008 n = 171	1.19 (0.91–1.56) *P*=.21 n = 270	0.97 (0.68–1.37) *P*=.85 n = 179	0.62 (0.14–2.72) *P*=.53 n = 14	.016	0.90 (0.82–0.98) *P*=.020 n = 1,189	1.37 (1.16–1.63) *P*=.0003 n = 505	1.23 (0.92–1.63) *P*=.16 n = 218	1.56 (0.74–3.30) *P*=.24 n = 35	<.0001	.16
Small for gestational age	0.78 (0.64–0.95) *P*=.013 n = 538	1.16 (1.00–1.34) *P*=.051 n = 970	0.92 (0.76–1.12) *P*=.42 n = 634	0.37 (0.15–0.93) *P*=.035 n = 42	.013	0.82 (0.79–0.85) *P*<.0001 n = 7,352	1.20 (1.11–1.29) *P*<.0001 n = 2,741	1.23 (1.08–1.41) *P*=.0024 n = 1,014	1.37 (0.96–1.97) *P*=.085 n = 178	<.0001	<.0001
Birth weight ≥4,500 g	1.32 (0.99–1.75) n = 280	0.88 (0.73–1.08) n = 536	1.23 (0.96–1.57) n = 363	1.35 (0.60–3.05) n = 46	.088	1.24 (1.18–1.30) *P*<.0001 n = 5,184	1.23 (1.14–1.33) *P*<.0001 n = 2,713	0.92 (0.79–1.06) *P*=.25 n = 903	0.94 (0.58–1.50) *P*=.78 n = 109	<.0001	.034
Perinatal mortality ≥28 wk	0.88 (0.48–1.61) n = 55	1.04 (0.67–1.61) n = 100	0.93 (0.57–1.50) n = 67	0.93 (0.57–1.50) n = 7	.96	0.92 (0.82–1.05) *P*=.22 n = 638	1.55 (1.24–1.94) *P*=.0001 n = 302	0.95 (0.70–1.30) *P*=.75 n = 119	0.95 (0.70–1.30) *P*=.75 n = 14	.0001	.93

Note: Odds ratios are based on piecewise logistic regression.

Wennberg. Age and obstetrical outcome in ART. Fertil Steril 2016.