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Smoking and Clinical Outcomes of Assisted Reproductive Technologies

Karilynn Rockhill, MPH^{1,2}, Van T. Tong, MPH¹, Sheree L. Boulet, DrPH¹, Yujia Zhang, PhD¹, Denise J. Jamieson, MD, MPH¹, and Dmitry M. Kissin, MD, MPH¹

¹Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Reproductive Health, Atlanta, Georgia.

²Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee.

Abstract

Background: Smoking near conception has adverse effects on pregnancy outcomes. We estimated the proportion of assisted reproductive technology (ART) cycles with smoking reported and associated clinical outcomes.

Methods: We used a retrospective cohort study (2009–2013) using national data of ART cycles in the United States. We compared patient characteristics, infertility diagnoses, and treatment procedures by self-reported smoking in the 3 months before treatment. Using multivariable logistic regression accounting for clustering by state, clinic, and patient, we assessed adjusted odds ratios (aOR) and 95% confidence intervals (CI) between smoking and clinical outcomes: cycle cancellations among all cycles (cycle stopped before retrieval of eggs or transfer of embryos), treatment outcomes (implantation, ectopic pregnancy, intrauterine pregnancy, and live birth) among cycles with 1 fresh embryo transferred, and pregnancy outcomes (miscarriage, stillbirth, and live birth) among intrauterine pregnancies.

Results: Smoking was reported in 1.9% of cycles. Higher proportions of cycles among smokers versus non-smokers were younger, non-Hispanic White, multigravida women and had tubal factor and male factor infertility diagnoses; lower proportions had diagnoses of diminished ovarian reserve and unexplained infertility, and used donor eggs. Smoking was associated with higher adjusted odds of cycle cancellation with no embryo transfer (aOR: 1.10; 95% CI: 1.00–1.21) and cancellations before fresh oocyte retrieval or frozen embryo transfer (1.11; 1.02–1.21). Associations between other clinical outcomes were nonsignificant.

Conclusions: Over 12,000 ART cycles in the United States were exposed to smoking during 2009–2013; smoking increased the odds of cycle cancellation. Providers should encourage women to quit smoking before ART treatments.

Address correspondence to: Van Tong, MPH, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Reproductive Health, CDC-Chamblee Campus, 4770 Buford Highway, NE, MS F-74, Atlanta, GA 30341-3717, vct2@cdc.gov.

Disclosure Statement

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Keywords

smoking; assisted reproductive technologies; pregnancy outcomes; cycle cancellations

Introduction

Smoking around the time of conception and during pregnancy has adverse effects, including reduced fertility, ectopic pregnancy, low birth weight, and preterm birth.^{1,2} Since 1981, there has been a steady increase in the number of assisted reproductive technology (ART) procedures performed in the United States.³ ART procedure success is a priority that depends not only on patient and treatment characteristics, but also on behavioral factors, such as smoking.⁴ Many population-based research studies have included ART patients who had a live birth, but fewer studies have looked at the effects between smoking and ART clinical outcomes. A meta-analysis found that smokers undergoing ART had significantly lower odds of clinical pregnancy and live birth per cycle, and significantly higher odds of ectopic pregnancy and miscarriage per pregnancy.⁵ Many prior studies had sample sizes inadequate to conduct sensitivity analyses, and were unable to properly adjust for fertility-related confounders, two important limitations stated in the smoking and infertility committee opinion.⁶ The associations between smoking and ART clinical outcomes have not been examined using population-based data.

In the United States, over 160,000 ART procedures were performed in 2013.⁷ The National ART Surveillance System collects data on ART treatments from all U.S. states and territories, as well as data on daily smoking intensity in the 3 months before treatment began. Using a large population-based dataset, we sought to evaluate the associations between smoking and selected ART clinical outcomes, specifically, smoking before ART increases likelihood of adverse outcomes during the cycle of treatment or early in pregnancy, and whether it is associated with later pregnancy outcomes. We also examined association by smoking intensity.

Materials and Methods

Data source and study population

The National ART Surveillance System (NASS) collects cycle-specific data on all fertility treatments (*i.e.*, *in vitro* fertilization and related procedures) from U.S. clinics, as mandated by the Fertility Clinic Success Rates and Certification Act of 1992 (Public Law 102–493).⁸ The data obtained cover approximately 98% of all ART procedures in the United States.³ Data accuracy is verified by clinic directors before submitting to the Centers for Disease Control and Prevention (CDC). Each year data from a sample of participating clinics are validated by comparison to medical records. Surveillance data include patient demographics, medical history, infertility diagnoses, treatment procedures, and clinical outcomes. Although data are organized as one record per cycle, patients at each clinic are assigned a unique identification number unless they switch clinics, where they would be assigned a different identification number. This study included data on all ART treatments performed between 2009 and 2013 in all U.S. states and territories.

Variables

History of smoking was ascertained by patient's report of lifetime smoking ("Has this patient smoked at least 100 cigarettes during entire life?"), and report of any smoking and number of cigarettes smoked per day in the 3 months before treatment began ("During the 3 months before this cycle started, did the patient smoke any cigarettes?/If patient smoked cigarettes during the 3 months before this cycle, on average, how many cigarettes per day did the patient usually smoke during those 3 months?"). Smokers were defined as women who reported any smoking in the 3 months before the cycle began, with intensity being classified based on the distribution of average daily number of cigarettes smoked: <1 cigarette/day (nondaily smoking), 1–5 cigarette(s)/day, 6–10 cigarettes/day, and 11 or more cigarettes/day. For initial analyses, we combined nonsmokers and former smokers (report of lifetime smoking and no smoking in the 3 months before treatment). We conducted sensitivity analyses excluding former smokers, which were similar to our main findings.

Clinical outcome data are provided for every cycle. Treatment and pregnancy outcomes of interest included:

1. Cancellation: ART procedures that were initiated but did not result in embryo transfer (cycle was stopped before eggs were retrieved or before embryos were transferred), including cancellations before fresh retrieval or frozen transfer, cancellations after retrieval and before transfer of embryos, and cycles with zero embryos transferred
 - a. Subset: Cancellation before fresh retrieval or frozen transfer only
2. Implantation rate: proportions defined as maximum number of fetal heart beats on ultrasound at 6 weeks of gestation or infants born if fetal hearts missing divided by the total number of embryos transferred, multiplied by 100; logistic regression and chi-square tests used binary classification of implantation (presence of fetal heart beat) versus no implantation
3. Ectopic pregnancy: fertilized eggs that implant outside the uterine cavity, including all heterotopic pregnancies
4. Intrauterine pregnancy: pregnancies confirmed by ultrasound of a gestational sac within only the uterus or documented occurrence of a pregnancy outcome, not including heterotopic pregnancies
5. Live birth: at least one fetus showed signs of life after the complete expulsion or extraction from the woman
6. Miscarriage: clinical pregnancies ending in loss before 20 weeks gestation
7. Stillbirth: delivery at 20 weeks gestation or later in which no fetus showed signs of life at birth

Patient characteristics examined include patient age, race/ethnicity, gravidity, number of prior miscarriages, and number of prior ART procedures. Infertility diagnoses examined include male factor, tubal factor (tubal ligation and other tubal disease), endometriosis, uterine factor, ovulatory disorder, diminished ovarian reserve, and unexplained infertility.

Treatment characteristics include year of treatment, cycle type (fresh cycles intended to transfer embryos derived from oocytes retrieved during the current cycle and frozen cycles intended to transfer embryos that were cryopreserved during a previous cycle), oocyte/embryo source (nondonor cycles intended to transfer embryos derived from the patient, and donor cycles intended to transfer donated embryos or oocytes), use of assisted hatching (micromanipulation technique to enhance implantation), use of intracytoplasmic sperm injection (placement of a single sperm into the ooplasm of an oocyte), day of embryo transfer (day 2–3 cleavage stage, day 5–6 blastocyst stage, or other), and number of embryos transferred.

Analysis

We restricted the analysis to cycles initiated between 2009 and 2013, where no gestational carrier was used and no embryo banking was performed ($N = 749,977$). We compared the distribution of demographic characteristics, infertility diagnoses, and treatment procedures by smoking status using chi-square tests. We calculated the proportion of each clinical outcome by smoking status and by smoking intensity; differences by smoking intensity were calculated using Wald chi-square tests. We estimated crude and adjusted odds ratios (aOR) using multivariable logistic regression to assess associations between smoking and clinical outcomes adjusting for potential confounders as fixed effects and accounting for clustering of cycles by patient, clinic, and state using random effects.

To examine cycle cancellations, we examined effects of smoking status on all cycles resulting in no embryo transfer and a subset cancelled before fresh retrieval or frozen transfer. Since we do not have information on the smoking status from the cycles in which frozen embryos originated, we conducted a stratified subanalysis using an interaction term for fresh and frozen transfer in the regression analyses. Confounders included were year of treatment, maternal age, gravidity, number of prior ART procedures, cycle type, oocyte/embryo source, and the following infertility diagnoses: tubal factor, endometriosis, uterine factor, ovulatory dysfunction, diminished ovarian reserve, male factor infertility, and unexplained infertility. For the subset of cycle cancellations before fresh retrieval or frozen transfer, we examined the reasons for cancellations reported by smoking status.

For other clinical outcomes, we restricted analyses to fresh cycles only, since we have the smoking status in the 3 months before the start of the cycle in which the embryo originated. To examine the effects of smoking status on treatment outcomes (implantation, ectopic pregnancy, intrauterine pregnancy, and live birth), we restricted analysis to cycles resulting in the transfer of at least 1 fresh embryo. To examine the effects of smoking status on pregnancy outcomes (miscarriage, stillbirth, and live birth), we restricted analysis to cycles resulting in intrauterine pregnancies only.

For all adjusted regression analyses, we controlled for demographics, infertility diagnoses, and treatment procedures, which could affect outcomes of an embryo transfer: use of assisted hatching, use of intracytoplasmic sperm injection, day of embryo transfer, and number of embryos transferred. To examine association with ectopic pregnancy, tubal ligations was also included as a confounder but not all tubal factor infertility, as tubal factors such as tubal disease may be on the causal pathway from smoking to ectopic pregnancy.⁹

Finally, history of prior miscarriage was also included as a confounder to examine association of miscarriage.

Approximately 14.5% of cycles had missing data on smoking status due to the screener question regarding lifetime smoking being left blank or reported as “Unknown.” To address the potential bias of missing data, we used a weighted analysis approach for both crude and aORs, as outlined in methods by Kissin et al.,¹⁰ based on the outcome distribution for those observations missing smoking. We first computed odds ratios without weighting, assuming smoking was missing at random, and then computed weighted odds ratios. Since the weighted results were similar to the unweighted results, we presented our weighted findings to account for missing smoking status.

Two sensitivity analyses were conducted to account for unobserved characteristics that might affect treatment outcome: (1) ART outcomes among only women under 40 years; and (2) ART outcomes among only the first cycle a patient underwent in our dataset, excluding subsequent cycles. We analyzed first cycles to eliminate any potential residual effect of several attempts but no longer accounted for clustering by patient since each patient was only represented once in the data.

Data were analyzed in SAS 9.3 callable SUDAAN Version 11. Statistical significance was set to $p < 0.05$. To maintain confidentiality, cell counts less than five have been suppressed, but is included in totals. This study was approved by the Institutional Review Board at CDC.

Results

From 2009 to 2013, there were 749,977 ART cycles, which represented approximately 422,621 patients. On average, patients underwent 1.77 cycles, with the number of cycles over the course of the 5-year study period ranging from 1 to 22 cycles per patient. Of total cycles, 113,636 (15%) cycles resulted in no embryo transfer, 189,734 (25%) were excluded based on frozen cycle type and 2,391 (<1%) due to missing cycle type, resulting in 444,236 fresh embryo transfers (Fig. 1). Of fresh transfers, 207,300 cycles (47%) resulted in intrauterine pregnancies. The proportion of missing data on smoking across all cycles included ($N = 108,553$, 14.5%) did not differ by reporting years, but cycles with missing smoking status were more likely to be among patients with more previous pregnancies, and had lower proportions of patients who had been diagnosed with ovulation disorders or whose partners had male factor infertility.

Overall, smoking in the 3 months before treatment was reported in 1.9% of cycles. Higher proportions of cycles among smokers, compared with cycles among nonsmokers, occurred in the earlier years and to patients who were younger, were non-Hispanic White, were multigravida, had diagnoses of tubal factor (including higher proportions of both tubal ligations and other tubal disease), and whose partners had male factor infertility; however, cycles among smokers had lower proportions of patients who had diagnoses of diminished ovarian reserve and unexplained infertility, and used donors as the oocyte/embryo source compared with cycles among nonsmokers (Table 1).

Cycle cancellation before retrieval or embryo transfer occurred in 15.7% and 15.1% of cycles among smokers and nonsmokers, respectively (Table 2). Fresh cycles had higher proportions of cancellations than frozen cycles. After adjustment, smoking before treatment was associated with significantly elevated odds of cancellation resulting in no embryo transfer (aOR: 1.10; 95% confidence interval (CI): 1.00–1.21; p -value = 0.04). After stratification, smoking was marginally associated with elevated odds of cancellation for fresh cycles (aOR: 1.11; 95% CI: 1.00–1.23; p -value = 0.05); however, among frozen cycles, smoking was not significantly associated with cancellation resulting in no embryo transfer (aOR: 1.07; 95% CI: 0.89–1.28; p -value = 0.46). In the model, with the exception of prior ART and uterine factor infertility, all other confounders were statistically significant.

Among the subset of cancellations before a fresh retrieval or frozen transfer, 9.1% and 8.5% of cycles were among smokers and nonsmokers, respectively (Table 2). After adjustment, cycles among smokers had an 11% increased odds of cancellation compared with cycles among nonsmokers (aOR: 1.11; 95% CI: 1.02–1.21, p -value = 0.02). When stratified by cycle type, the odds of cancellation before a fresh retrieval was 1.14 times higher among smokers compared with nonsmokers (95% CI: 1.04–1.26, p -value = 0.01). Again, no effect was found by smoking status on cancellations before a frozen transfer. Overall, the reasons for cancelling a cycle did not differ by smoking status. The three most common reasons reported for cycle cancellations among smokers and nonsmokers, respectively, were: low ovarian response (68.3% vs. 65.9%, p = 0.19), withdrawal for personal reasons (14.8% vs. 15.8%, p = 0.49), and inadequate endometrial response (9.2% and 9.6%, p = 0.68).

Among all cycles resulting in the transfer of at least one fresh embryo, implantation rates were 27.2% and 27.9% among smokers and nonsmokers, respectively. Ectopic pregnancies among smokers and nonsmokers were 1.0% and 0.9%, respectively. Almost half of cycles resulted in an intrauterine pregnancy, irrespective of smoking status (smokers: 45.3%; nonsmokers: 46.6%) and just over one-third resulted in a live birth (smokers: 37.2%; nonsmokers: 38.4%) (Table 2). After adjustment, we found no statistically significant association between smoking status in the 3 months before treatment and implantation (aOR = 0.92, 95% CI: 0.83–1.02), intrauterine pregnancy (aOR = 0.92, 95% CI: 0.83–1.03), live birth (aOR = 0.92, 95% CI: 0.84–1.02), or ectopic pregnancy (aOR = 1.14, 95% CI: 0.89–1.46).

Among all cycles resulting in an intrauterine pregnancy, regardless of smoking status, around 16% of cycles resulted in a miscarriage, <1% resulted in a stillbirth, and around 83% resulted in live birth (Table 2). After adjustment, we did not find statistically significant association between smoking before treatment and live birth (aOR = 0.96, 95% CI: 0.87–1.05) and miscarriage (aOR = 1.05, 95% CI: 0.96–1.15) and stillbirth (aOR = 1.03, 95% CI: 0.66–1.59).

There was evidence of a dose/response relationship between daily smoking intensity before treatment and cycle cancellations. As daily smoking intensity increased, the proportion of cancellations resulting in no embryo transfer increased (p = 0.04) and the proportion of cancellations before fresh retrieval or frozen transfer increased (p = 0.04), with elevated proportions at 1–5 cigarette(s)/day (Table 3, Fig. 2). Among fresh cycles, almost one in five

cycles were cancelled resulting in no embryo transfer among patients smoking six or more cigarettes/day (Table 3). We did find statistically significant differences in the distribution of implantation, intrauterine pregnancy, and live birth by smoking intensity, but potential dose/response patterns could not be discerned. The distributions of ectopic pregnancy, spontaneous miscarriage, and stillbirth by smoking intensity did not reach statistical significance.

Among cycles to women under 40 years, 2.0% reported smoking in the 3 months before treatment. Significant associations found were between smoking status and cycle cancellation resulting in no embryo transfer (weighted aOR = 1.11; 95% CI: 1.00–1.23; *p*-value = 0.04) and the subset of cancellations before fresh retrieval or frozen transfer (weighted aOR = 1.13; 95% CI: 1.03–1.25; *p*-value = 0.01). Among only first cycles, 2.1% of patients reported smoking in the 3 months before treatment. Only the subset of cancellations before fresh retrieval or frozen transfer were associated with smoking status (weighted aOR = 1.13; 95% CI: 1.02–1.25; *p*-value = 0.02). No other associations were statistically significantly different in the sensitivity analyses.

Discussion

Over 12,000 ART cycles (1.9% of total treatments) in the United States are potentially exposed to smoking over our 5-year study period. Compared with cycles among non-smokers, cycles among smokers had a 10% increased odds of cycle cancellation before retrieval or embryo transfer and an 11% increased odds of cancellation before fresh retrieval and frozen transfer after adjustment. Smoking before a fresh oocyte retrieval showed 1.14-fold higher odds of cancellation. There also appeared to be a dose/response relationship with daily smoking intensity and cancellations: almost one in five fresh cycles resulted in no embryo transfer for patients smoking six or more cigarettes per day. Once a fresh embryo transfer occurred, our aOR point estimates, although not statistically significant, showed smoking reduced the odds of implantation, intrauterine pregnancy, and live birth, and increased the odds of having an ectopic pregnancy. These findings were consistent to a meta-analysis of effects between smoking and ART outcomes using data from clinic populations⁵; however, there are many differences across study designs and findings across ART studies should be compared with caution.

Since our study was based on self-reported smoking, underreporting of smoking and overreporting of quitting cannot be ruled out,¹¹ which may bias our results toward the null. Smoking cessation rates are estimated to be 50% in general pregnant population data¹²; however, smoking status after treatment began or during pregnancy was unavailable in our dataset. Assuming similar cessation rates among the ART population, misclassification of smoking status could also bias our results toward the null. Providers should continue to encourage women to enter ART treatments completely tobacco free, as smoking cessation represents an important part of effective treatment for infertility.⁶

We found that 1.9% of cycles were among patients who reported smoking in the 3 months before treatment. Even when accounting for about two cycles per women, this estimate is much lower than the 17.1% smoking prevalence in the general U.S. population of women of

similar age (25–44 years old).¹³ This low prevalence of self-reported smoking before ART treatment likely represent a special population of women actively trying to become pregnant. It has been estimated that 13% of infertility is attributable to cigarette smoking,¹⁴ which leads women to seek ART treatment. Providers should still advise women that smoking may decrease their chances of becoming pregnant with ART.

One strength of this U.S. population-based study is having the sample size and covariates necessary to control for confounding based on demographic characteristics, infertility diagnoses, and treatment procedures. Previous studies utilized small samples, and may not be representative of the total ART population. This study does have several limitations. First, smoking data in this study are self-reported and not biochemically verified. Because of the known effects of smoking on fertility and smokers being excluded from receiving ART treatment coverage,¹ women undergoing ART may underreport their true smoking habits, potentially mis-classifying smoking status, and biasing our results toward the null. An analysis of linked NASS data and birth certificate data from two states found that the NASS data ascertained more smokers than the birth certificate.¹⁵ Furthermore, because data on smoking after ART was not available, we were not able to assess whether it confounded the relationship with later pregnancy outcomes. Second, we lacked power in several of our outcomes (*e.g.*, ectopic pregnancies, still birth) to discern an effect, also with our analysis of smoking intensity given the low prevalence of smoking in ART users. Third, the ART surveillance data do not include partner smoking status or secondhand smoke exposure.^{5,16} Finally, 14.5% of our data had missing smoking status due to missing or unknown lifetime smoking. We accounted for this through a weighted regression approach based on distribution of outcomes for those with known smoking status. This approach corrects missing data bias and yields larger standard errors in parameter estimation, resulting in more conservative results.

Conclusions

Over 12,000 ART cycles in the United States had reported smoking in the 3 months before ART treatment began during 2009–2013. Smoking increased odds of cycle cancellation and may decrease the chance of a successful pregnancy with ART. Providers should discuss the effects of smoking on infertility and benefits of smoking cessation, and provide support and effective interventions that will help women enter ART treatments tobacco free.

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FIG. 1.

Flow chart of study inclusion criteria. The flow chart does not take into account missing smoking status in 14.5% of cycles. Both crude and adjusted analysis uses a weighted analysis approach based on the outcome distribution for those observations missing smoking, with the assumption that smoking was missing at random.

FIG. 2.

ART cycle cancellations by smoking intensity, National ART Surveillance System, 2009–2013. Among cycles not using a gestational carrier nor banking ($N = 641,277$). A potential dose/response relationship was observed between intensity of smoking in the 3 months before treatment and cycle cancellations and subset of those cancelled before fresh retrieval or frozen transfer; based on Wald chi-square tests. ART, assisted reproductive technology

Table 1.

Treatment and Patient Characteristics for Assisted Reproductive Technology Cycles by Smoking Status, National Assisted Reproductive Technology Surveillance System, 2009–2013

	<i>Nonsmoking No. (%)</i>	<i>Smoking No. (%)</i>	<i>p (χ²)</i>
Patient factors			
Patient age (years)			0.01
<30	69,961 (11.1)	1,625 (13.3)	
30–34	183,491 (29.2)	3,763 (30.8)	
35–37	127,854 (20.3)	2,560 (21.0)	
37	247,928 (39.4)	4,262 (34.9)	
Race/Ethnicity			<0.01
Non-Hispanic White	295,253 (46.9)	6,607 (54.1)	
Non-Hispanic Black	30,183 (4.8)	388 (3.2)	
Non-Hispanic Asian	59,109 (9.4)	447 (3.7)	
Hispanic	34,977 (5.6)	541 (4.4)	
Other	1,139 (0.2)	13 (0.1)	
Unknown/Missing	208,573 (33.1)	2,414 (34.5)	
Number of previous pregnancies			<0.01
0	249,720 (39.8)	4,184 (34.3)	
1	175,319 (27.9)	3,263 (26.7)	
2 or more	202,834 (32.3)	4,759 (39.0)	
Number of previous spontaneous miscarriages			0.05
0	417,288 (66.6)	7,819 (64.2)	
1	131,230 (21.0)	2,641 (21.7)	
2 or more	77,781 (12.4)	1,711 (14.1)	
Number of prior ART cycles			0.19
0	268,462 (42.7)	5,513 (45.2)	
1	160,728 (25.6)	3,103 (25.4)	
2 or more	199,679 (31.8)	3,592 (29.4)	
Infertility diagnosis ^a			
Tubal factor	90,187 (14.3)	3,040 (24.9)	<0.01

	<i>Nonsmoking No. (%)</i>	<i>Smoking No. (%)</i>	<i>p</i>	<i>(χ^2)</i>
Endometriosis	63,187 (10.0)	1,279 (10.5)	0.42	
Uterine factor	31,536 (5.0)	646 (5.3)	0.60	
Ovulatory dysfunction	92,513 (14.7)	1,863 (15.3)	0.52	
Diminished ovarian reserve	186,436 (29.6)	2,951 (24.2)	0.02	
Male factor	222,345 (35.3)	4,908 (40.2)	<0.01	
Unexplained infertility	78,421 (12.5)	1,051 (8.6)	<0.01	
ART treatment procedure				
Year of treatment				<0.01
2009	114,836 (18.3)	3,138 (25.7)		
2010	120,162 (19.1)	2,555 (20.9)		
2011	125,660 (20.0)	2,237 (18.3)		
2012	131,356 (20.9)	2,222 (18.2)		
2013	137,220 (21.8)	2,058 (16.9)		
Oocyte/embryo source				0.01
Nondonor	556,937 (88.8)	11,098 (91.2)		
Donor	70,090 (11.2)	1,069 (8.8)		
Cycle type				0.13
Fresh	454,536 (72.5)	9,019 (74.1)		
Frozen	172,491 (27.5)	3,148 (25.9)		
Use of assisted hatching ^b	235,943 (44.1)	4,719 (45.9)	0.54	
Use of ICSI ^c	316,125 (75.6)	6,396 (79.1)	0.08	
Day of embryo transfer ^d				0.98
Cleavage stage (2–3 days)	170,866 (45.9)	3,385 (46.1)		
Blastocyst stage (4–5 days)	164,486 (44.1)	3,224 (43.9)		
Other	37,421 (10.0)	730 (9.9)		
Number of embryos transferred				0.08
1	116,968 (21.9)	2,073 (20.1)		
2	295,398 (55.3)	5,762 (56.0)		
3	88,135 (16.5)	1,830 (17.8)		
4 or more	34,021 (6.4)	625 (6.1)		

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Data are presented as column percent.

Among cycles which did not use a gestational carrier and no embryo banking with nonmissing smoking status ($N = 641,444$).

^a Infertility diagnoses are not mutually exclusive.

^b Not applicable for cycles that are cancelled or do not result in embryo transfers.

^c Not applicable for cycles that are cancelled, frozen cycles, or processed with gamete intrafallopian transfer.

^d Number of days between retrieval and transfer; not applicable for frozen cycles or cycles where no embryo was transferred. ART, assisted reproductive technology; No., number of cycles; ICSI, intracytoplasmic sperm injection.

Prevalence and Association of Clinical Outcomes Among Assisted Reproductive Technology Cycles by Smoking Status, National Assisted Reproductive Technology Surveillance System, 2009–2013

Table 2.

Clinical outcomes	Nonsmoking No. (%)	Smoking No. (%)	Crude OR (95% CI) ^d		Adjusted OR (95% CI) ^d	
			REF:nonsmoking		REF:nonsmoking	
Total cycles (<i>N</i> = 641,444) ^{b,c}						
Cancelled cycle resulting in no embryo transfer	94,712 (15.1)	1,920 (15.7)	1.05 (0.95–1.16)		1.10 (1.00–1.21) ^d	
Fresh cycles	81,974 (18.0)	1,681 (18.6)	1.04 (0.94–1.16)		1.11 (1.00–1.23) ^d	
Frozen cycles	12,511 (7.3)	234 (7.4)	1.03 (0.87–1.21)		1.07 (0.89–1.28)	
Subset: Cancelled cycle before fresh retrieval or frozen transfer	53,512 (8.5)	1,112 (9.1)	1.08 (0.98–1.19)		1.11 (1.02–1.21) ^d	
Fresh cycles	43,181 (9.5)	926 (10.3)	1.09 (0.98–1.21)		1.14 (1.04–1.26) ^d	
Frozen cycles	10,236 (5.9)	182 (5.8)	0.98 (0.81–1.18)		0.98 (0.82–1.17)	
Cycles resulting in at least 1 fresh embryo transfer (<i>N</i> = 379,633) ^e						
Implantation ^f	162,834 (27.9)	3,092 (27.2)	0.94 (0.84–1.06)		0.92 (0.83–1.02)	
Ectopic pregnancy	3,255 (0.9)	71 (1.0)	1.11 (0.87–1.41)		1.14 (0.89–1.46)	
Intrauterine pregnancy	173,495 (46.6)	3,318 (45.3)	0.95 (0.84–1.06)		0.92 (0.83–1.03)	
Live birth	143,107 (38.4)	2,729 (37.2)	0.95 (0.86–1.05)		0.92 (0.84–1.02)	
Cycles resulting in an intrauterine pregnancy (<i>N</i> = 175,885) ^e						
Spontaneous miscarriage	26,914 (15.6)	523 (15.9)	1.02 (0.95–1.09)		1.05 (0.96–1.15)	
Stillbirth	1,020 (0.6)	21 (0.6)	1.08 (0.69–1.67)		1.03 (0.66–1.59)	
Live birth	143,041 (82.9)	2,727 (82.7)	0.99 (0.92–1.06)		0.96 (0.87–1.05)	

Data are all presented as a column percent.

^aWeighted crude OR accounting for clustering by patient, clinic, and state using random effects. Models for cycle type stratification also included an interaction term.

^bAmong cycles not using a gestational carrier nor embryo banking with nonmissing smoking status (*N* = 641,444) stratified by cycle type: subanalyses included known fresh cycles (*N* = 463,555) and frozen cycles (*N* = 175,639).

^cWeighted OR adjusted for year of treatment, maternal age, gravidity, number of prior ART procedures, cycle type, oocyte/embryo source, tubal factor, endometriosis, uterine factor, ovulatory dysfunction, diminished ovarian reserve, male factor infertility, and unexplained infertility as fixed effects and accounting for clustering by patient, clinic, and state using random effects. Models for cycle type stratification also included an interaction term.

^pStatistically significant odds ratios based on $p < 0.05$.

^gWeighted OR adjusted for year of treatment, maternal age, gravidity, number of prior ART procedures, cycle type, oocyte/embryo source, tubal factor, endometriosis, uterine factor, ovulatory dysfunction, diminished ovarian reserve, male factor infertility, unexplained infertility, use of assisted hatching, use of intracytoplasmic sperm injection, day of embryo transfer, and number of embryos transferred as fixed effects and accounting for clustering by patient, clinic, and state using random effects. Models for ectopic pregnancy included tubal ligations as a fixed effect but not all tubal disease, since tubal disease was thought to be on the causal pathway from smoking to ectopic pregnancy. Models for spontaneous miscarriage also included history of prior spontaneous miscarriage as a fixed effect.

^fImplantation analyses compares any known implantation to no implantation ($N = 368,595$); whereas the proportion was defined as maximum number of fetal hearts or infants born divided by the total number of embryos transferred, multiplied by 100.

OR, odds ratio; No., number of cycles; CI, confidence interval; REF, reference group.

Table 3.

Prevalence of Clinical Outcomes Among Assisted Reproductive Technology Cycles by Daily Smoking Intensity (Cigarette(s)/day), National Assisted Reproductive Technology Surveillance System, 2009–2013

Clinical outcomes	Nonsmoking		Nondaily <1		1–5		6–10		11		p-value
	No. (%) with outcome	No. (%)with outcome	No. (%)with outcome	No. (%) with outcome	No. (%) with outcome	No. (%) with outcome	No. (%) with outcome	No. (%) with outcome			
Total cycles (N = 641,277) ^a											
Cancelled cycle resulting in no embryo transfer	94,712 (15.1)	392 (12.3)	642 (16.0)	721 (17.9)	141 (17.3)	0.040 ^b					
Fresh	81,974 (18.0)	301 (15.3)	583 (18.5)	650 (20.5)	123 (20.7)	0.238					
Frozen	12,511 (7.3)	91 (7.4)	59 (7.0)	68 (8.1)	16 (7.4)	0.922					
Subset: Cancelled cycle before fresh retrieval or frozen transfer	53,512 (8.5)	221 (6.9)	360 (9.0)	445 (11.1)	73 (9.0)	0.041 ^b					
Fresh	43,181 (9.5)	161 (8.2)	311 (9.9)	382 (12.1)	59 (9.9)	0.184					
Frozen	10,236 (5.9)	60 (4.9)	49 (5.8)	61 (7.3)	12 (5.6)	0.408					
Cycles resulting in at least 1 fresh emryo transfer (N = 379,519)											
Implantation ^c	162,834 (27.9)	706 (27.0)	1,117 (28.6)	1,001 (25.4)	218 (30.4)	0.017 ^b					
Ectopic pregnancy	3,255 (0.9)	17 (1.0)	20 (0.8)	27 (1.1)	7 (1.5)	0.552					
Intrauterine pregnancy	173,495 (46.6)	765 (45.8)	1,189 (46.4)	1,079 (42.9)	233 (49.5)	0.032 ^b					
Live birth	143,107 (38.4)	613 (36.7)	1,004 (39.2)	881 (35.0)	187 (39.7)	0.010 ^b					
Cycles resulting in intrauterine pregnancy (N= 175,834)											
Spontaneous miscarriage	26,914 (15.6)	136 (17.9)	165 (14.0)	173 (16.2)	43 (18.5)	0.237					
Stillbirth	1,020 (0.6)	<i>d</i>	6 (0.5)	9 (0.8)	<i>d</i>	0.637					
Live birth	143,041 (82.9)	613 (80.7)	1,004 (84.9)	880 (82.2)	186 (79.8)	0.196					

Data are all presented as a column percent.

^a Among cycles not using a gestational carrier nor banking with nonmissing smoking intensity ($N = 641,277$), stratified by cycle type: subanalyses among known fresh cycles ($N = 463,417$) and frozen cycles ($N = 175,616$).

^b Statistically significant based on Wald chi-square test, $p < 0.05$.

^c Implantation analyses compares any implantation to no implantation ($N = 368,483$); whereas the proportion was defined as maximum number of fetal hearts or infants born divided by the total number of embryos transferred, multiplied by 100.

^d Cell counts less than five have been suppressed to maintain confidentiality.

No., number of cycles.

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