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Denise V. D'Angelo
Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia, ddangelo@cdc.gov

Nedra Whitehead
RTI International, Research Triangle Park, North Carolina

Kristen Helms
Science Applications International Corporation, San Diego, California

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

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

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Denise V. D'Angelo, M.P.H.,[a] *Nedra Whitehead, Ph.D., M.S.,*[b] *Kristen Helms, M.S.P.H.,*[c] *Wanda Barfield, M.D., M.P.H.,*[a] *and Indu B. Ahluwalia, M.P.H., Ph.D.*[a]

[a] Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia; [b] RTI International, Research Triangle Park, North Carolina; and [c] Science Applications International Corporation, San Diego, California

Objective: To study birth outcomes among live born infants conceived by women who used infertility treatment.
Design: Population-based surveillance of women who recently delivered a live infant.
Setting: The birth outcomes among infants whose mothers used assisted reproductive technology (ART) or ovulation stimulation medications alone were compared with the outcomes of infants conceived without treatment.
Patient(s): Stratified random sample of women who were attempting conception and gave birth to a live infant in six US states (n = 16,748).
Intervention(s): Assisted reproductive technology and ovulation stimulation.
Main Outcome Measure(s): Adjusted odds ratios for perinatal outcomes.
Result(s): The prevalence of infertility treatment use overall among women attempting conception was 10.9% (5.4% ART procedures, 5.5% ovulation stimulation medications). Singletons of mothers who received ART procedures were more likely to be born with low birthweight, preterm, and small for gestational age (SGA) than singleton infants conceived without treatment. Singleton infants of mothers who used ovulation stimulation medications alone were more likely to be SGA than singleton infants conceived without treatment. No differences were found between ART and no treatment twin infants.
Conclusion(s): Among singleton infants, ART is associated with decreased fetal growth, decreased gestational length, and SGA; ovulation stimulation alone is associated with SGA. (Fertil Steril® 2011;96:314–20. ©2011 by American Society for Reproductive Medicine.)

Key Words: PRAMS, pregnancy, infertility, ovulation stimulation, assisted reproductive technology (ART), infant birth outcomes

Use of infertility treatments, such as assisted reproductive technology (ART) procedures and ovulation stimulation medications without ART, has increased dramatically in the United States. Assisted reproductive technology includes treatments in which both the oocyte and the sperm are handled in the laboratory. Medications to stimulate ovulation are used in ART procedures before retrieval of oocyte; however, these medications can also be used for non-ART treatments. From 1997–2000, the annual number of ART infants born increased by 44% (1). In 2006, about 1% of all US births were to women who had undergone ART procedures (2). Assisted reproductive technology use has been associated with an elevated risk of pregnancy complications for the mother and adverse outcomes for the infant, with the most common complication being multiple gestation (1–6). According to data from the US ART Surveillance System, 49% of 2006 ART births were multiple gestation births compared with only 3% multiple gestation for all US births (2, 7). Infants born as multiples have an increased risk of preterm delivery, low birthweight, infant mortality, and long-term disability (8–10).

In addition to problems associated with multiple gestation deliveries, studies have found that singleton ART-conceived infants are more likely to be low birthweight compared with singletons whose mothers did not use ART (11–14). Some studies have also found a greater risk of birth defects among singletons and multiples conceived using ART compared with those conceived without treatment (15–18); however, the evidence is inconsistent and suggests that risk may be related to underlying infertility (19–21). Concern about long-term sequelae of ART use, such as neurodevelopmental problems, has been identified as an area needing further research (22–25).

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Reprint requests: Denise V. D'Angelo, M.P.H., Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, 4770 Buford Highway, NE Mailstop K-22, Atlanta, Georgia 30341 (E-mail: DDAngelo@cdc.gov).

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TABLE 1

Prevalence of selected characteristics by infertility treatment status, six PRAMS states, 2000–2003.

Characteristic	ART (n = 920)		Medication only (n = 904)		No treatment (n = 14,673)	
	%	95% CI	%	95% CI	%	95% CI
Plurality[a]						
Singleton	75.5	71.5, 79.5	93.4	91.7, 95.1	98.8	98.6, 99.0
Twin	22.1	18.2, 26.0	5.9	4.3, 7.5	1.2	1.0, 1.4
Triplet	2.4	1.6, 3.2	0.7	0.3, 1.1	0.0	−0.01,0.03
Maternal characteristics						
Age[a]						
<25 y	2.4	0.8, 4.0	11.2	8.1, 14.3	22.5	21.5, 23.5
25–34 y	56.2	51.0, 61.4	68.2	63.6, 72.7	62.6	61.5, 63.8
≥35 y	41.4	36.2, 46.6	20.6	16.8, 24.5	14.8	14.1, 15.6
Race[a]						
White	88.5	85.1, 91.9	90.3	87.4, 93.3	85.5	84.7, 86.4
Black	6.5	3.8, 9.1	4.4	2.5, 6.3	8.9	8.2, 9.6
Other	5.0	2.8, 7.3	5.3	2.9, 7.6	5.6	5.0, 6.1
Ethnicity[a]						
Non-Hispanic	94.9	92.5, 97.4	90.2	87.1, 93.4	84.7	83.8, 85.7
Hispanic	5.1	2.6, 7.5	9.8	6.6, 12.9	15.3	14.3, 16.2
Marital status[a]						
Married	94.7	92.3, 97.1	92.0	89.1, 94.9	84.3	83.4, 85.2
Other	5.3	2.9, 7.7	8.0	5.1, 10.9	15.7	14.8, 16.6
Education[a]						
<12 y	2.8	1.0, 4.6	6.8	3.9, 9.6	13.3	12.4, 14.1
12 y	15.6	11.6, 19.6	20.2	16.3, 24.1	24.4	23.4, 25.5
>12 y	81.6	77.3, 85.9	73.1	68.6, 77.5	62.3	61.1, 63.5
Parity[a]						
Primiparous	53.8	48.5, 59.1	51.3	46.3, 56.2	40.1	38.9, 41.2
≥1 child	46.2	40.9, 51.5	48.7	43.8, 53.7	59.9	58.8, 61.1
Income[a]						
<Median	21.2	16.0, 26.3	29.3	23.7, 34.8	44.7	43.2, 46.1
≥Median	78.8	73.7, 84.0	70.8	65.2, 76.3	55.3	53.9, 56.8
Birth interval						
≤6 mo	3.0	0.8, 5.2	2.7	0.9, 4.5	2.9	2.4, 3.3
>6 to <24 mo	26.5	20.7, 32.2	28.0	22.6, 33.4	30.6	29.3, 31.9
≥24 mo	70.6	64.7, 76.5	69.3	63.8, 74.8	66.5	65.2, 67.9
Multivitamin use before pregnancy[a]						
≥4 times/wk	81.0	76.8, 85.2	70.1	65.7, 74.5	48.0	46.8, 49.2
0–3 times/wk	19.0	14.8, 23.2	29.9	25.5, 34.3	52.0	50.8, 53.2
Cigarette smoking last trimester of pregnancy[a]						
No	96.8	95.0, 98.6	97.3	95.8, 98.7	91.3	90.6, 92.0
Yes	3.2	1.4, 5.0	2.7	1.3, 4.2	8.7	8.0, 9.4
Alcohol consumption last trimester of pregnancy						
No	91.0	87.7, 94.3	94.2	91.9, 96.6	94.0	93.4, 94.5
Yes	9.0	5.7, 12.3	5.8	3.4, 8.1	6.0	5.5, 6.6
Body mass index[a]						
Underweight (<19.8)	10.9	7.6, 14.2	9.6	6.7, 12.4	12.3	11.5, 13.1
Normal (19.8–26)	57.1	51.7, 62.4	51.5	46.4, 56.5	55.2	54.0, 56.4
Overweight (26–29)	9.1	6.3, 11.9	12.5	9.1, 15.9	12.9	12.1, 13.7
Obese (>29)	22.9	18.3, 27.6	26.5	22.1, 30.9	19.6	18.6, 20.5
Infant outcomes						
Birthweight[a]						
≥2,500 g	77.9	74.9, 80.8	89.4	87.7, 91.0	94.3	94.1, 94.5
1,500–2,499 g	17.2	14.7, 19.8	8.6	7.1, 10.0	4.6	4.3, 4.8
<1,500 g	4.9	3.7, 6.1	2.1	1.4, 2.7	1.1	1.0, 1.3
Gestational age[a]						
≥37 wk	69.9	65.5, 74.3	85.0	82.3, 87.8	91.4	90.8, 91.9
<37 wk	30.1	25.7, 34.5	15.0	12.2, 17.7	8.6	8.1, 9.2
SGA[a,b]						
No	85.5	82.0, 89.0	88.9	85.9, 91.8	93.3	92.7, 93.8
Yes	14.5	11.0, 18.0	11.1	8.2, 14.1	6.7	6.2, 7.3

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TABLE 1

Continued.

Characteristic	ART (n = 920) %	ART (n = 920) 95% CI	Medication only (n = 904) %	Medication only (n = 904) 95% CI	No treatment (n = 14,673) %	No treatment (n = 14,673) 95% CI
Hospital stay[a]						
<5 days	77.4	73.5, 81.2	87.5	84.9, 90.1	91.3	90.6, 91.9
≥5 days	22.6	18.8, 26.5	12.5	9.9, 15.1	8.7	8.1, 9.4
NICU[a]						
No	77.1	73.2, 81.1	85.2	82.1, 88.3	89.8	89.1, 90.4
Yes	22.9	18.9, 26.8	14.8	11.7, 17.9	10.2	9.6, 10.9
Infant death[a]						
No	98.8	98.1, 99.4	99.6	99.4, 99.9	99.4	99.3, 99.6
Yes	1.2	0.6, 1.9	0.4	0.1, 0.6	0.6	0.4, 0.7

Note: SGA = small for gestational age; NICU = neonatal intensive care unit; ART = assisted reproductive technology; CI = confidence interval; PRAMS = Pregnancy Risk Assessment Monitoring System.

[a] Characteristic is significantly different between treatment groups (χ^2 test, $P<.05$).

[b] SGA was calculated accounting for infant race, sex, gestational age, and birthweight among black and white infants. Infants with missing data on any of these items or with race designated as "other" were excluded.

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Although research has been focused on the laboratory component of ART, the effect of ovulation stimulation medications alone has been less well studied. Birth outcomes among infants of mothers who used ovulation stimulation medications without ART is an important group to consider given that a recent study estimated that 4.6% of US infants born in 2005 were conceived as a result of non-ART ovulation stimulation (26). In addition, there is some evidence that superovulation can affect DNA methylation, causing imprinting changes, which can effect fetal growth and development (27).

The purpose of this study was to examine infant outcomes among women who reported using either ART or ovulation stimulation medications without around the time of conception using a large population-based sample. We used data from the Pregnancy Risk Assessment Monitoring System (PRAMS), which allowed us to investigate and control for multiple maternal characteristics, behaviors, and lifestyle factors, as well as differentiate ART and ovulation stimulation outcomes.

MATERIALS AND METHODS

PRAMS is a population-based surveillance system of maternal and infant health indicators funded in part by the Centers for Disease Control and Prevention and administered by state health departments. The unit of analysis for PRAMS is the woman who delivered a live birth. Mothers of twins and triplets are sampled once, and these women report on the health of one of their infants who is randomly selected at the time of sampling. The PRAMS does not sample women who give birth to multiples beyond triplets. The data are weighted for sample design, nonresponse, and noncoverage to represent all women who delivered a live birth in each participating PRAMS state for each calendar year. Details on the PRAMS methodology have been published previously (28), and are available from the PRAMS web site http://www.cdc.gov/prams. The Centers for Disease Control and Prevention Institutional Review Board approved the PRAMS protocol and all participating states approved the study plan.

We analyzed data from six states (Alabama, Illinois, Maine, Maryland, Nebraska, and Oklahoma) selected because they were the only PRAMS states to collect data on the use of both ART and ovulation stimulation medications from 2000–2003. We used 2000–2003 data for this analysis because these specific infertility measures were only available on the PRAMS survey during those years. Overall weighted response rates for each state were 70% or greater for each year of data. In the PRAMS questionnaire structure, only women who reported they were trying to become pregnant answered the questions on infertility treatment use. Therefore, our analysis was restricted to women who were attempting a pregnancy. In the absence of other fertility-related variables in the dataset (such as time to pregnancy), this subgroup of women constituted an appropriate population to study differences between birth outcomes of women who used infertility treatments and those who did not.

The PRAMS dataset included variables linked from the birth certificate (1989 standard birth certificate) and variables from the questionnaire. We obtained information on maternal age, race, ethnicity, education level, marital status, parity, plurality, infant gestational age, birthweight, and other medical risk factors (identified by a dichotomous indicator) from the birth certificate. We used PRAMS questionnaire data on maternal prepregnancy height and weight, multivitamin use, and smoking and alcohol consumption during the third trimester of pregnancy. The dependent variable in the analysis was birth outcome (birthweight, gestational age, small for gestational age (SGA), length of infant hospital stay after birth, admission to the neonatal intensive care unit (NICU), and infant death (between the time of the live birth and survey response). One percent or less of the data for the outcome variables was missing, with the exception of birthweight (<4%). SUDAAN software was used for the analysis to account for PRAMS' complex sampling design and statistical weighting (29). More detail on the study methods can be found in Supplemental Table 1.

There were 35,848 respondents in the dataset representing 1,351,718 women who delivered a live infant in six states during 2000–2003; 16,748 reported they were trying to get pregnant with their new baby and were included in the analysis. There were 251 women (1.5%) with missing information on use of infertility treatment who were excluded from the analysis. Among the remaining 16,497 women, 15,406 gave birth to singleton infants, 980 to twins, and 111 to triplets. We did not examine differences in birth outcomes among triplet infants separately because of small numbers; however, mothers of triplet infants are included in the prevalence estimates in Table 1.

RESULTS

Overall, 1,824 (10.9%) women who were trying to become pregnant reported using infertility treatment. There were 920 (5.5%) women who reported using ART, 904 (5.4%) women who reported use of ovulation stimulation medications alone, and 14,673 (87.6%) women who reported no infertility treatment.

There were significant differences by infertility treatment status for the following maternal characteristics: age, race, ethnicity, marital status, education, parity, income, multivitamin use before

pregnancy, cigarette smoking in the last trimester of pregnancy, and prepregnancy body mass index (BMI). There were no differences in alcohol consumption during pregnancy or birth interval (among multiparous women) (Table 1).

Infant Outcomes

The prevalence of adverse infant outcomes increased with the use of more intensive treatment. Women using ART were at the highest risk and those not using any treatment were at the lowest risk. This pattern is evident not only in the overall sample (Table 1), but also when restricted to singleton infants (Table 2). Among singleton infants, there was a significant difference in the prevalence of low birthweight (very low birthweight and low birthweight combined was 9.8% of the ART group, 6.5% for the medication-only group, and 5.1% for the no treatment group). Preterm birth (<37 weeks gestation) was also highest among the ART group (16.1%), followed by the medication-only group (11.0%), and lowest in the no treatment group (8.0%). The pattern is similar for SGA, infant hospital stay longer than 5 days, and infant spending time in the NICU, although long hospital stay and NICU admission were not statistically significant (Table 2). All of the affected infants in the study had more than one study outcome.

Among mothers of singleton infants, those who used ART were more than twice as likely to have a low birthweight infant (crude odds ratio [cOR]: 2.10, confidence interval [CI]: 1.58, 2.79) as women who did not undergo any treatment. Mothers who used ART were almost two times more likely to give birth before 37 weeks gestation (cOR: 1.94, CI: 1.42, 2.65) and more likely to have an SGA infant (cOR: 1.72, CI: 1.13, 2.61). Their infants were also significantly more likely to spend 5 or more days in the hospital (cOR: 1.49, CI: 1.04, 2.14), and more likely to be admitted to the NICU (cOR: 1.53, CI: 1.12, 2.24). There was no significant difference in very low birthweight or infant death (Table 3).

In the adjusted analysis, we looked among singletons only at outcomes that were significant in the unadjusted analysis described previously. Women who used ART were more than two times as likely to have a low birthweight singleton infant (adjusted OR [AOR]: 2.20, CI: 1.55, 3.13). ART use was also associated with preterm birth (AOR: 1.91, CI 1.31, 2.80) and delivering an SGA infant (AOR: 1.98, CI: 1.21, 3.24) (Table 3). For hospital stay of 5 days or more, there were interactions with parity, age, and BMI. Further analysis showed no significant association for primiparous women. Only the relationship among multiparous young women with low or normal BMI was significant; however, the estimate is imprecise (AOR: 9.30, CI: 3.18, 27.19) (Table 4). For admission to the NICU, we found interactions with parity and age. Again, there was no association for primiparous women. However, for multiparous young women, we found an association between ART use and NICU admission with an imprecise estimate (AOR: 7.16, CI: 3.23, 15.87) (Table 4).

Comparing mothers of singleton infants who used ovulation stimulation medications without ART to women who received no treatment, those who used ovulation stimulation medications alone were significantly more likely to have an SGA infant (cOR: 1.59, CI: 1.11, 2.27) than women who received no treatment. In the adjusted analysis, this association remained significant (AOR: 1.71, CI: 1.09, 2.69) (Table 3).

Among twin births, there were no significant differences in any of the infant outcomes that we examined when comparing ART users with women who received no treatment. Nor did we find any

TABLE 2

Prevalence of birth outcomes among singletons by infertility treatment status, six PRAMS states, 2000–2003.

	ART		Medication only		No treatment	
Infant outcome	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**
Birthweight[a]						
≥2,500 g	90.2	88.0, 92.4	93.5	92.2, 94.8	94.9	94.7, 95.1
1,500, 2,499 g	8.0	6.0, 10.0	5.2	4.1, 6.3	4.1	3.9, 4.3
<1,500 g	1.8	1.0, 2.6	1.3	0.8, 1.9	1.0	0.9, 1.1
Gestational age[a]						
≥37 wk	83.9	79.7, 88.1	89.0	86.4, 91.6	92.0	91.5, 92.5
<37 wk	16.1	11.9, 20.3	11.0	8.4, 13.6	8.0	7.5, 8.6
SGA[a,b]						
No	89.3	85.4, 93.2	90.0	86.9, 93.1	93.5	93.0, 94.0
Yes	10.7	6.8, 14.6	10.0	6.9, 13.1	6.5	6.0, 7.0
Hospital stay						
<5 d	88.0	84.3, 91.7	90.1	87.5, 92.7	91.6	91.0, 92.2
≥5 d	12.0	8.3, 15.7	9.9	7.3, 12.5	8.4	7.8, 9.0
NICU						
No	85.3	80.9, 89.5	87.4	84.2, 90.6	90.2	89.5, 90.9
Yes	14.7	10.5, 19.1	12.6	9.4, 15.8	9.8	9.2, 10.6
Infant death						
No	99.6	99.2, 100.0	99.7	99.5, 99.9	99.5	99.4, 99.6
Yes	0.4	0, 0.8	0.3	0.1, 0.54	0.5	0.4, 0.6

Note: SGA = small for gestational age; NICU = neonatal intensive care unit; ART = assisted reproductive technology; CI = confidence interval; PRAMS = Pregnancy Risk Assessment Monitoring System.

[a] Characteristic is significantly different between treatment groups (χ^2, $P<.05$).

[b] SGA was calculated accounting for infant race, sex, gestational age, and birthweight among black and white infants. Infants with missing data on any of these items or with race designated as "other" were excluded.

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TABLE 3

Association between use of ART or ovulation stimulation medications and infant outcomes among singleton infants, six PRAMS states, 2000–2003.

	ART				Medication only			
Infant outcome	cOR	95% CI	AOR[a]	95% CI	cOR	95% CI	AOR[b]	95% CI
Birthweight								
≥2,500 g	Ref		Ref		Ref		Ref	
1,500–2,499 g	2.10	1.58, 2.79	2.20	1.55, 3.13	1.26	0.99, 1.62	—	—
<1,500 g	1.41	0.95, 2.10	—	—	1.27	0.81, 1.97	—	—
Gestational age								
≥37 wk	Ref		Ref		Ref		Ref	
<37 wk	1.94	1.42, 2.65	1.91	1.31, 2.80	1.23	0.95, 1.63	—	—
SGA[b]								
No	Ref		Ref		Ref		Ref	
Yes	1.72	1.13, 2.61	1.98	1.21, 3.24	1.59	1.11, 2.27	1.71	1.09, 2.69
Hospital stay								
<5 d	Ref		Ref		Ref			
≥5 d	1.49	1.04, 2.14	c	c	1.20	0.89, 1.63	—	—
NICU								
No	Ref		Ref		Ref			
Yes	1.53	1.12, 2.24	d	d	1.32	0.98, 1.78	—	—
Infant death								
No	Ref		Ref		Ref			
Yes	0.81	0.34, 1.90	—	—	0.56	0.25, 1.23	—	—

Note: cOR = crude odds ratio; SGA = small for gestational age; ART = assisted reproductive technology; CI = confidence interval; PRAMS = Pregnancy Risk Assessment Monitoring System.

[a] Adjusted odds ratio: adjusted for age, race, ethnicity, marital status, income, smoking, alcohol use, education, parity, prepregnancy body mass index, state of residence, medical risk factors.

[b] SGA was calculated accounting for infant race, sex, gestational age, and birthweight among black and white infants. Infants with missing data on any of these items or with race designated as "other" were excluded.

[c] Interaction with parity, age, and body mass index, see Table 4.

[d] Interaction with parity and age, see Table 4.

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significant differences in twin outcomes comparing women who used ovulation stimulation medications without ART with women who received no treatment. However, many of the effect sizes were large among the medication-only group, possibly indicating a relationship, but inconclusive due to the small sample size (data not shown).

DISCUSSION

Overall, 10.9% of the women in our study used infertility treatment. This is higher than other reports because our study was restricted to women who were trying to become pregnant, rather than the entire birth population (2). We confirmed the previously reported relationship that singleton infants born to mothers who undergo ART procedures are more likely to be low birthweight (11–15), preterm (13, 14, 30), or SGA (13, 30, 31) than singleton infants born to mothers who did not undergo treatment. We further provide one of a few studies of this size and diversity showing an association between the use of ovulation stimulation medications without ART and infants being born small for gestational age for singleton infants. Although the literature on twin outcomes is inconsistent, our study using a large population-based sample corroborates the findings of a number of studies that do not note any difference among outcomes of twin infants born after ART compared with spontaneously conceived twins (11, 30, 32). Our findings relative to ovulation stimulation-only twins were inconclusive.

Our findings suggest a relationship between ART use and the risk of an infant's hospital stay of 5 or more day and NICU admission for multiparous women less than 35 years of age. Other studies have found increased NICU admission for singleton ART births, and longer hospitalizations for ART infants (33, 34, 36), but not specific to younger women. There is some evidence that increased maternal morbidity and infant low birthweight linked with ART use may be associated with poor gamete quality, or other factors related to the maternal or paternal subfertility rather than the ART procedures. The research in this area is inconclusive and the exact mechanism responsible for the difference in infant outcomes has not been identified (13, 21, 35, 37, 38). Although the confidence intervals around our estimates for these indicators are wide, the findings may suggest that the cause of underlying infertility is playing a role in the increased use of hospital services among some ART singleton infants. These younger, multiparous women may be more likely to have an underlying cause of infertility that could affect fetal growth or development.

We found that mothers who reported using ovulation stimulation medications without ART were more likely to have an infant that was small for gestational age compared with infants who were conceived without treatment. Other studies have also linked ovulation stimulation with adverse infant outcomes such as prematurity and low birthweight, but not specifically SGA (35, 36).

TABLE 4

Association between use of ART, infant hospital stay of 5 or more days and NICU admission, six PRAMS states, 2000–2003.

Maternal characteristic	Infant hospital stay ≥5 d		NICU admission	
	AOR[a]	95% CI	AOR[a]	95% CI
Primiparous				
Age <35 y			1.23	0.62, 2.07
BMI ≤26	2.13	0.95, 4.80	—	—
BMI >26	0.46	0.17, 1.22	—	—
Age ≥35 y			1.15	0.50, 2.63
BMI ≤26	0.81	0.27, 2.49	—	—
BMI >26	0.55	0.18, 1.69	—	—
Multiparous				
Age <35 y			7.16	3.23, 15.87
BMI ≤26	9.30	3.18, 27.19	—	—
BMI >26	0.29	0.07, 1.17	—	—
Age ≥35 y			1.35	0.46, 3.99
BMI ≤26	1.43	0.41, 4.93	—	—
BMI >26	1.60	0.37, 6.94	—	—

[a] Adjusted odds ratio: adjusted for age, race, ethnicity, marital status, income, smoking, alcohol use, education, parity, prepregnancy body mass index, state of residence, medical risk factors.

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There are several limitations to this study. Although we controlled for state of residence in our regression analysis, the data are from six states selected based on their use of the PRAMS questions on infertility, and findings are not generalizable to other states or the entire United States. The PRAMS data on use of ART and ovulation stimulation medications are self reported in the postpartum period. A validation study by Schieve et al in 2006 (39) found that using the infertility questions from 2000–2003, PRAMS overestimates the number of ART births when compared with estimates from the US ART Surveillance System suggesting that women might be reporting past use of treatments. We do not have information on the treatment used, on the underlying cause of infertility, or on other potentially confounding factors such as gamete quality. And, although the questions refer to the most recent pregnancy, we do not know whether the procedures or medications directly resulted in the pregnancy with the infant about whom the woman is being surveyed.

Despite these limitations, PRAMS provides a large population-based sample that enables examination of multiple infant outcomes, and an appropriate comparison group of other women who reported they were actively trying to get pregnant, which is more similar to those women who use ART than the population of all women delivering a live birth. The availability of multiple covariates from the PRAMS survey allows for the use of robust approaches to identify and control for possible confounding variables.

The use of infertility treatments has become increasingly common in the United States, and risks go beyond multifetal pregnancies. The findings from this study add to the growing body of literature on the use of infertility treatments and the safety of these treatments for the infants that are conceived. Considering the elevated risks, especially for singleton births from ART and ovulation stimulation medications alone, couples who are considering treatment should be counseled on potential risks to their singleton infants, in addition to the increased risk of having a multiple birth as the result of ART or ovulation stimulation medications.

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SUPPLEMENTAL TABLE 1

PRAMS methodology and indicators.

PRAMS methodology

In each state that conducts PRAMS, a stratified random sample of women who recently gave birth to a live infant is drawn from state birth certificate records 2–6 months after birth. Data are collected by mailed questionnaire and nonrespondents are followed up by telephone. The data are weighted for sample design, nonresponse, and noncoverage to represent all women who delivered a live birth in each participating PRAMS state for the calendar year. Mothers of multiples are eligible to be sampled only once for their delivery. Assessment of infant—the experiences for these women is based on the outcomes of one of their infants who is randomly selected at the time of sampling. The randomization for twins is as follows: if the birth date lies between the first and fifteenth of the month, the first-born twin is sampled; otherwise the second-born twin is sampled.

PRAMS infertility treatment indicators (2000–2003)

"**Did you take any fertility drugs to help you get pregnant with your new baby?** (Fertility drugs include Clomid, Serophene, Pergonal, or any other drugs that you may have taken to help you get pregnant.)"

No

Yes

"**Did you use any medical procedures (assisted reproductive technology [ART]) to help you get pregnant with your new baby?** (Assisted reproductive technology [ART] procedures include IVF, GIFT, zygote intrafallopian transfer [ZIFT], ET, and donor oocytes.)"

No

Yes

A woman was considered to have used ovulation stimulation medications if she answered "yes" to the first question and "no" to the second question. A woman was considered to have used assisted reproductive technology (ART) if she answered "yes" to both questions. Women who answered "yes" only to the second question were included in the ART group.

Definition of Birth Outcomes

Small for gestational age (SGA): SGA was calculated using an algorithm that accounted for infant race, sex, gestational age, and birthweight among black and white infants. Infants with missing data on any of these items or with race designated as "other" were excluded from the SGA analysis.

Birthweight: Birthweight was separated into three categories, normal birth weight ($\geq$2,500 g), low birthweight (1,500–2,499 g), and very low birthweight ($<$1,500 g).

Gestational age: Gestational age was determined from the date of the last menstrual period (LMP) and clinical gestational age from the birth certificate, using the algorithm described by Alexander et al. (1). If gestational age could not be determined by LMP or clinical week, we calculated it from the infant's date of birth and the due date from the questionnaire. Records with incompatible infant birthweight and gestational age, based on the criteria used by Adams et al. (2), were excluded. We defined preterm birth as gestational age $<$37 weeks.

Body mass index (BMI): BMI was calculated using 1990 Institute of Medicine categories based on self-reported prepregnancy height and weight from the questionnaire (3).

Definition of covariates

Medical risk: Medical risk was identified by a dichotomous indicator on the birth certificate if the mother had any one of 16 possible chronic or pregnancy-induced conditions such as anemia, eclampsia, or hypertension (4).

Statistical methods

Bivariate analysis: We examined the characteristics of women who used ART, ovulation stimulation medications alone, and those who did not use infertility treatments by calculation of percentages and 95% confidence intervals. We tested for differences between the characteristics of these groups using χ^2 tests (significance defined as $P<.05$).

Multivariate analysis

Unadjusted analysis: We examined the unadjusted relationship between infant health outcomes and infertility treatments by calculating crude odds ratios with 95% confidence intervals.

*Adjusted analysis:*We further examined health outcomes that were significantly associated with infertility treatment in the crude analysis using logistic regression to adjust for other factors related to the birth outcomes. We then used a hierarchical modeling reduction process to eliminate variables that neither interacted with nor confounded the relationship of interest. We eliminated variables from the model that did not interact with or confound the relationship between infertility treatment and infant health outcomes. We identified significant interactions using the likelihood ratio test. We defined a confounding variable as one that changed the estimate of the relationship of the infertility treatment and health outcomes by 10% or more.

Covariates: We used a theory-driven process of choosing covariates based on their previously identified association with birth outcomes. We examined age, parity, prepregnancy BMI, and presence of a medical risk factor for interactions with infertility treatment. We examined state of residence, maternal age, race, ethnicity, marital status, income, smoking during pregnancy, drinking during pregnancy, maternal education, parity, BMI, and medical risk factor as potential confounders.

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