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Perinatal Outcomes Associated with Assisted Reproductive Technology: the Massachusetts Outcomes Study of Assisted Reproductive Technologies (MOSART)

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Abstract

Objective—To compare on a population basis the birth outcomes of women treated with Assisted Reproductive Technologies (ART), women with indicators of subfertility but without ART, and fertile women.

Design—Longitudinal cohort study

Setting—Massachusetts

Participants—334,628 births and fetal deaths to Massachusetts mothers giving birth in a Massachusetts hospital between July 1, 2004–December 31, 2008, subdivided into three subgroups for comparison: ART 11,271, subfertile 6,609, and fertile 316,748.

Intervention—None

Main Outcome Measures—Four outcomes: preterm birth, low birthweight, small for gestational age and perinatal death, were modeled separately for singletons and twins using

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logistic regression with the primary comparison between ART births and those to the newly created population based subgroup of births to women with indicators of subfertility but no ART.

Results—Singletons: The risks for both preterm birth and low birthweight were higher for the ART group (AOR 1.23 and 1.26, respectively) compared to the subfertile group and risks in both the ART and subfertile groups were higher than those among fertile births. Twins: the risk of perinatal death was significantly lower among ART births than fertile (AOR 0.55) or subfertile (AOR 0.15) births.

Conclusions—The use of a population based comparison group of subfertile births without ART demonstrated significantly higher rates of preterm birth and low birthweight in ART singleton births, but these differences are smaller than differences between ART and fertile births. Further refinement of the measurement of subfertile births and examination of the independent risks of subfertile births is warranted.

Keywords

Assisted Reproductive Technologies; Subfertility; Preterm Birth; Low Birthweight; Perinatal Death

INTRODUCTION

In the U.S. in 2012, treatment with assisted reproductive technologies (ART) resulted in 51,267 live births (deliveries of one or more living infants) and 65,160 live born infants representing 1.6% of all U.S. births(1). The growth in the use of ART has raised concerns about a range of perinatal outcomes in the resulting births, including the excess of preterm birth,(2–4) low birthweight,(5–7) small for gestational age(8) and neonatal death.(9) However, research into such outcomes has faced several major constraints:(10) randomization to ART treatment is not feasible; studies from individual ART clinics may lack statistical power; and population based, vital records datasets often lack accurate measurement of ART treatment. Importantly, most studies of outcomes of ART have not distinguished the effect of ART from that of underlying infertility.(10, 11) The outcomes of ART births have been analyzed in comparison to spontaneous conceptions,(12–14) across different treatment parameters,(15) within women themselves across different pregnancies(16) and, within a survey population,(17) to measures of delay in becoming pregnant. In the U.S. context, a population based comparison group of births to women with indicators of subfertility without ART has not been available for comparison in the past.(18) This study utilized a linkage between state records in a national ART clinical database and a statewide longitudinally linked public health database to develop a population based comparison group of births to women with indicators of subfertility who did not receive ART, thus permitting examination of underlying risks associated with these births and providing a more refined assessment of the unique impact of ART on perinatal outcomes.

METHODS

STUDY DATA

Data Sources—This study linked detailed clinical information on ART treatment from all ART clinics in Massachusetts with live births and fetal deaths from July 1, 2004 through December 31, 2008 recorded in the Massachusetts Pregnancy to Early Life Longitudinal (PELL) Data System. Both the PELL (19) and Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS)(20, 21) data systems have been described in previous publications. PELL links data on more than 99% of all births and fetal deaths in Massachusetts from 1998–2009 to corresponding hospital utilization data (admissions, outpatient stays and emergency room visits) and then longitudinally links those data over time, facilitating analysis of maternal hospitalizations prior to a given birth or fetal death. The SART CORS collects data from more than 400 ART clinics across the U.S. (covering 97% of all ART cycles).(22) The SART database includes all Massachusetts clinics, providing the opportunity for a population based examination of outcomes in the state. The national SART CORS database for 2004–08 contains 642,927 records of assisted reproductive technology treatment cycles. The database includes information on demographic characteristics, infertility diagnoses, treatment parameters, treatment outcomes and pregnancy outcomes.

Approval for the study was granted by the Institutional Review Boards at the Massachusetts Department of Public Health and the Boston University School of Medicine as well as the institutions of the project's co-principal investigators.

Linkage of the Data Sources—We constructed the Massachusetts Outcomes Study of Assisted Reproductive Technologies (MOSART) database by linking the SART CORS and PELL data systems for all children born to Massachusetts resident women in Massachusetts hospitals between July 1, 2004 and December 31, 2008. The starting date was chosen based on the start date of our access to SART CORS (January 1, 2004) to allow us to capture any births associated with ART and the end date reflected the latest available data from both SART and PELL. PELL data from July 1, 2004 through December 31, 2008 included 282,971 women with 334,152 singleton or twin deliveries resulting in 342,035 births and fetal deaths which were linked to 42,649 ART cycles among 18,439 women from SART CORS with a resultant linkage of PELL delivery records to 9,092 ART cycles. We limited our analysis to singletons or twins with complete data on the predictors and outcomes of interest. The linkage process has been previously described. (23)

ANALYSIS

ART group—ART deliveries were identified from the SART CORS database drawing on clinical data from all Massachusetts infertility clinics. We identified 11,271 live births and fetal deaths from 9,092 deliveries.

Subfertility with no ART Comparison Group—The subfertility comparison group was developed using an algorithm that conservatively identified births to women with indicators of subfertility. The goal was to include only cases in which we had clear

indication of either diagnosis of infertility through diagnosis codes or maternal report of fertility assistance. The method, which has been described in detail elsewhere, (18) involved identification of subfertile deliveries from three sources:

1. birth certificates – inclusion if either one of two items on the Massachusetts birth certificate concerning the use of fertility drugs or ART were checked for a delivery from July 1, 2004– December 31, 2008 *or* on a certificate for an earlier birth to the same woman in the five years prior to an index pregnancy in 2004–2008; or
2. prior hospital utilization – inclusion if a woman had hospital contact – admission, observational stay or emergency department visit – for a condition specifically indicating infertility (ICD codes 628.0/628.2/628.3/628.8/628.9/V230) associated with an index delivery *or* in the five years prior to an index pregnancy occurring between 2004–2008. The 628 codes represent “Diminished or absent ability of a female to achieve conception... a term doctors use if a woman hasn’t been able to get pregnant after at least one year of trying.”(24) The V23.0 diagnosis code represents “Supervision of high-risk pregnancy with history of infertility.”(25)
3. prior ART – inclusion if a woman had an ART cycle in the past as reported to SART CORS between 2004–2008, but did not have an ART cycle associated with the index delivery between 2004–2008.

Prior to cross-checking to eliminate cases that were identified in more than one data set, each source yielded the following number of births: Birth Certificates (9,929); Hospital Utilization (3,321) and SART data (1,641). After eliminating duplication in multiple sources, there were 12,918 cases and after then excluding cases with documented ART use in the index delivery, there were 6,905 births that provided evidence of subfertility without an ART cycle identified in clinic records for that birth. Finally, after limiting our data to births with complete data, the subfertile group included 6,609 live births and fetal deaths to mothers with at least one indicator of infertility with no evidence of an ART cycle for that birth.(18)

Fertile Comparison Group—Births not included in either the ART or Subfertile categories were classified as “Fertile,” since there was no indicator of subfertility or ART use. The Fertile group included 316,748 live births and fetal deaths.

Outcome Measures—Our final analysis was limited to cases with complete data for the variables used in the multivariate model. All analyses were stratified by plurality (singletons and twins) and examined across the three groups of interest. The perinatal outcomes were preterm birth (<37 completed weeks of gestation); low birthweight (< 2500 gms); small for gestational age (lowest 10th percentile among birthweights); and perinatal death (fetal deaths plus neonatal deaths < 7 days).(26) Birthweight Z-scores were calculated to evaluate adequacy of weight for age using Massachusetts population-based standards. In order to determine small for gestational age (SGA) births, we generated gender-, race/ethnicity-, and gestation-specific birthweight means and standard deviations using Massachusetts data for all live births from 1998–2008. Infants with birthweights below the 10th percentile for gestation were classified as small-for-gestational age. We limited our analyses of preterm

birth, low birthweight and SGA to live births because of the differing distribution of birthweight by gestational age in fetal deaths (27) and the fact that the distribution used for determining SGA was based on live births only. Our linked data allowed us to identify each twin in a pair and perinatal deaths are based on the death of either twin in a pair.

Covariates—We conducted a series of analyses using logistic regression models to identify potential confounding variables in the association of fertility group and each outcome of interest. First, we ran a model with only the main independent factor, fertility status (as dummy variables, Subfertile vs. Fertile and ART- vs. Fertile). Subsequent models introduced each of the potential confounding variables starting with maternal socio-demographic characteristics. At each stage of modeling, we observed changes in the strength of association between fertility status and the outcome of interest. Variables that did not alter the associations (odds ratios) of either of the fertility group variables with outcome by 10% or more were not retained in the model.

The covariates that remained were maternal age, race/ethnicity, marital status, maternal education, payer for delivery, smoking, prenatal care,(28) parity, chronic and pregnancy associated hypertension, and infant gender. Individual maternal health conditions (e.g. endometriosis, polycystic ovaries, peritoneal adhesions) that were not captured in the subfertility measure were combined into a single dichotomous measure, “other fertility related condition,” which was included in the model. We tested for interaction effects between the main independent variable (fertility status of the delivery) and select demographic characteristics associated with each of the perinatal outcomes. None were deemed significant and as such were not included in the final models. We added propensity scores as covariates to our multivariate logistic models out of the concern that the processes which resulted in being categorized as fertile, subfertile or having received ART were potentially different.(29, 30) Inclusion of the propensity scores did not substantially alter the odds ratios, confidence intervals, or p-values and therefore were not included in the final model. In the multivariate logistic regression models we ran analyses of ART and subfertile outcomes compared to the fertile group, followed by a specific comparison of ART outcomes compared to subfertile births. The data were analyzed using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA.) and models computed using general estimating equations (GEE) to account for clustering of outcomes within a mother.

Results

Table 1 presents the demographic characteristics of the three fertility groups by plurality. The profile of ART and Subfertile births without ART were much more similar to each other than either group were to the cohort of fertile births. P values in the table are for the comparison of the ART and subfertile groups. Among singletons, mothers in the ART group were more likely to be older, better educated, have private insurance, be nulliparous, and have higher rates of pregnancy induced hypertension and primary cesarean section. Among twin births, mothers with ART tended to be older and more likely to deliver by primary cesarean section.

Table 2 presents the unadjusted prevalence of prematurity, birthweight, small for gestational age and perinatal death for the three fertility groups by plurality. Among singletons, ART births compared to subfertile births were more likely to be preterm (10.2% vs 8.1%), low birthweight (7.8% vs 5.7%) and small for gestational age SGA (8.1% vs 6.5%). Among twins, ART births compared to subfertile births had a longer mean gestational age (35.6 vs 35.0 weeks), lower rate of very premature (<32 weeks) delivery, (8.9% vs 11.6%), very low birthweight (< 1500 grams) births (7.7% vs 10.3%), and much lower rate of perinatal death (11.5 per 1,000 vs 61.5 per 1,000). The ART twin births had the lowest perinatal death rate of the three groups.(31) Comparing the perinatal death rates of singletons versus twins, we see a much smaller disparity between the ART populations (11.5 per 1,000 for twins versus 4.2 for singletons) compared to the difference in perinatal death rate between fertile twins (25.7) and singletons (4.3).

Figure 1 presents gestational age distributions by week for the three groups. Among singletons the ART group had higher proportions of births in weeks 32–37, though the modal week for ART births was week 40, while the subfertile group had a peak at 39 weeks. Among twins, the higher rate of early preterm births for the subfertile group is evident from a distinct tail at less than or equal to 27 weeks while the ART group had a lower rate of early preterm births than the fertile group.

Table 3 presents the adjusted odds ratios and 95% confidence intervals for each outcome by plurality for the three fertility groups controlling for the covariates noted above. We compared the ART and subfertile groups to the fertile group as the reference and then the ART group was compared directly to the subfertile group as a reference. Among singletons, the odds of preterm birth and low birthweight were higher among both the subfertile (AORs 1.24 and 1.20 respectively) and ART (1.53 and 1.51 respectively) groups compared to the fertile group, and the ART group was significantly higher than the subfertile group in each case (AOR 1.23 and 1.26 respectively). The risk for SGA among singletons did not differ significantly between the three fertility groups, nor between the ART and subfertile groups. The odds ratio for perinatal death among the ART group was comparable to the fertile group though the subfertile group had a significantly higher rate (AOR 1.51).

Among twin births, there were no significant differences in preterm birth or low birthweight across the three fertility groups. In the case of SGA, the risks for both the subfertile and ART groups were 15–20% lower than the fertile group; there was no difference between the ART and subfertile group. Compared to the fertile group, the subfertile group had a higher risk (AOR 3.73) of perinatal death, while the ART group had half the risk (AOR 0.55). (31, 32) Comparing the subfertile and ART groups, the latter had an 85% lower risk (AOR 0.15). Examination of the perinatal deaths among the subfertile twin births found a higher concentration of very premature births (84% of neonatal deaths prior to 24 weeks in the subfertile vs. 62% in ART group). When we tested models for twin perinatal death that included gestational age, the differences between the fertile and subfertile groups became non-significant, though the odds of a twin death in the ART group remained significantly lower than either the fertile or subfertile group (data not shown).

Sensitivity Analysis

We conducted a sensitivity analysis to examine the potential impact of the use of alternative measures of outcomes and to better understand the reasons behind particular findings. Using early neonatal death (<7 days) as an outcome (i.e. excluding fetal deaths), we found a similarly lower risk of deaths among ART twins compared to subfertile births (AOR 0.12) as in the analysis of perinatal death (AOR 0.15). We also examined whether or not ART births were more likely to have occurred in Level III hospitals and found larger proportions of both ART and “Subfertile without ART” twin births occurring in tertiary centers compared to fertile births. We then tested whether including a variable for hospital level in our models would alter the findings and it did not. One possible explanation for the better outcomes of ART twins could be the higher rate of dichorionic pregnancies among ART births(33, 34) which fare better than monochorionic births, a hypothesis our data do not permit us to examine directly since monozygosity is not recorded in either of our datasets. However, an analysis restricted to mixed gender twins – by definition dichorionic – found a comparable relative difference between subfertile and ART perinatal deaths (AOR 0.16) as the original model (AOR 0.15).

Discussion

There has long been concern(35) that perinatal outcomes associated with ART births may be compromised. This study has addressed several of the major problems that have limited past research efforts to examine perinatal outcomes, most notably the inability to distinguish between outcomes that may be the result of ART and those resulting from underlying infertility. In this study, we found that preterm birth and low birthweight were increased among ART singletons when compared to singleton deliveries in a fertile population, but that these were also increased in a subfertile population. Further, the risk of perinatal death for ART twins was much lower than in births to fertile mothers and lower still than to mothers with indicators of subfertility without ART.

An important contribution of this paper is the application of our initial approximation of a U.S. based population measure(18) of births to mothers with an indicator of subfertility who did not have an ART cycle associated with the index birth being studied. The addition of this group permits the examination of perinatal outcomes associated with infertility apart from ART as well as the comparison of outcomes associated with ART with those of births to mothers with and without indicators of subfertility. While a number of studies have examined the outcomes of births to mothers with subfertility indicators who gave birth without ART, these have generally been based on non-U.S. data sources(17, 36–38) or systematic reviews that primarily drew on non-U.S. studies.(4, 8) These studies generally found, as we did, higher rates of preterm birth and low birthweight among singleton births to women with indicators of subfertility independent of ART. The importance of the current work is to extend these comparisons to a US population in which ART treatment parameters including amount of ovulation stimulation medication and number of embryos transferred may be different than those of other countries.

Comparing the perinatal outcomes of ART births to spontaneous conceptions, our findings are largely consistent with past research that has found higher rates of preterm birth and low

birthweight among singletons born after ART. A meta-analysis by Jackson(13) and systematic reviews by Helmerhorst(12) and Allen(14) all found higher risks for preterm birth and low birth weight when comparing ART births to spontaneous conceptions. While rates of singleton preterm birth and low birth weight were significantly higher in this study, the degree of difference we found was lower than AORs for the same comparison in past research, which might be accounted for by our ability to include substantially more covariates (demographic, social and medical risk) than prior studies. Also, the time frame for our research is more recent than these prior studies and both Klemetti (39) and Kallen(40) reported ART results relative to spontaneous conceptions to be improving over time. Our findings differ somewhat with past findings on SGA. Our more contemporary, U.S. based analysis found no differences between SGA of ART and fertile singleton births, while some prior research(36) has found higher rates of SGA in both subfertile and ART assisted births.

Our findings on perinatal death are of particular interest. Among singletons, we found no difference in risk of perinatal death in births to mothers with ART when compared to births to fertile women while there was a significantly higher risk of perinatal death in the subfertile group without ART. Two prior studies examined perinatal mortality as an outcome in births to subfertile women without ART. Both Basso(9) and Draper(32), relying on different populations and measures of subfertility found, as we did, significantly higher neonatal or perinatal mortality in births to mothers with indicators of subfertility and no ART when compared to spontaneous conceptions (AORs both 3.3). Unlike our findings, both Jackson and Helmerhorst's reviews found higher rates of perinatal death for singleton ART births, but both drew a large proportion of cases from a single 1990's Belgian study (41) in which mortality rates were almost double current rates.

Outcomes of twin ART births fared better than comparable fertile births for SGA and perinatal death. These findings are generally consistent with past research, though the literature on outcomes of twin births is less extensive and was limited to the use of spontaneous conceptions as the comparison group.(42–45) Our finding of a lower rate of perinatal death among twins in ART births compared to those from fertile births is comparable to prior research by Fitzsimmons(45) and Boulet,(43) and closely matches the results of Helmerhorst's systematic review (AOR 0.58).(31) Our study, relying on state vital statistics data to identify fetal and early neonatal deaths benefitted from much larger populations than prior studies. One suggested explanation for the better outcomes is the "special baby" hypothesis, suggesting that the extra attention given to ART births by both parents and caregivers may contribute to more favorable outcomes.(46) ART mothers had higher rates of primary cesarean section and "adequate plus" prenatal care, though the differences in prenatal care with the "subfertility without ART" group were minimal (Table 1). Nonetheless it may be possible that ART related births involved greater attention to care and more sensitive and comprehensive measures of prenatal care than are currently available on a population basis will be necessary to determine if a "special baby" hypothesis is supported. Considering only the subfertile population, our study found notably higher risks for perinatal death among twins when compared to births to mothers without subfertility indicators. Overall these studies suggest an underlying risk associated with subfertility distinct from that which may result from ART.

Despite the advantages our linked dataset brings to the analysis, limitations remain. Massachusetts was chosen as a site for the study in part because of its policy of mandating private insurers to cover ART and the corresponding high rate of ART use, but the experience in Massachusetts may not be representative of other settings. Our algorithm used to identify “subfertile” births may have missed some cases, misclassifying them as “fertile.” The MOSART dataset does not yet have access to ambulatory care cases, hence those mothers seen by non-hospital healthcare providers for infertility treatment would be missed. As a result, subfertile cases identified through hospital discharge data likely represent an undercount of all cases of treatment for subfertility, though some of the ambulatory care cases were likely identified through the birth certificate items. Ambulatory subfertile patients may be less subfertile, than those found in the subfertile institution population. If true, this would tend to increase the significance of the results. We chose a conservative measure to maximize the positive predictive value of our subfertile designation and sought to avoid misclassification of fertile cases into the much smaller subfertility group.⁽¹⁸⁾ We were also unable to determine definitively how long mothers in the subfertile group had been trying to conceive and whether they conceived spontaneously or used fertility drugs or other non-ART procedures to conceive. Longer infertile intervals have been associated with a greater risk for adverse outcome. This may explain some of the differences between the ART and sub fertile groups. Likewise we were not able to assess time to pregnancy for women in the fertile group. However, our study question focused on the overall impact of the use of ART, rather than an explicit comparison between fertility drug use and ART.

The analysis of the perinatal outcomes of ART births in comparison to births to women with indicators of subfertility is a valuable step forward in our understanding of the reasons for adverse outcomes. Future research on the subfertility group itself can yield important information through refinement of the subfertility measure and further exploration of poor outcomes in this population. The enhancement of our understanding of the outcomes of assisted reproductive technologies will continue to provide information to help clinicians better inform patients of any risks associated with ART treatment.

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Figure 1.
Gestational Age Distribution, by Fertility Groups, Singletons & Twins

— FERTILE – Twin
 - - SUBFERTILE – Twin
 - - ART – Twin
 — FERTILE – Singleton
 — SUBFERTILE – Singleton
 — ART – Singleton

Table 1
Maternal and Paternal Characteristics of the Study Population by Maternal Fertility Status

	Singletons					Twins			
	FERTILE	SUBFERTILE – No ART	ART	ART vs Subfertile		FERTILE	SUBFERTILE – No ART	ART	ART vs Subfertile
N (Live births and fetal deaths)	308,103	5,552	6,480	P*		8,645	1,057	4,791	P*
	%	%	%	%		%	%		
Mother's Age					<0.01				<0.01
30 yrs	54.6	16.4	11.8			47.4	20.5	15.4	
31–34	24.2	29.3	27.0			26.9	35.2	28.9	
35–37	12.8	26.8	25.5			16.5	23.5	25.4	
38–40	6.2	18.2	20.8			7.2	15.0	17.0	
41–42	1.6	6.0	8.1			1.3	3.6	6.4	
43	0.7	3.4	6.9			0.8	2.7	7.0	
Mother Non-Hisp. White	67.3	85.0	86.0	<0.01		70.3	88.6	87.9	0.33
Mother BachDeg. Postgrad	40.6	69.8	74.0	<0.01		44.3	71.0	72.7	0.02
Mother U.S. Born	72.4	82.6	82.5	0.87		77.1	84.8	83.0	0.14
Mother Not Married	33.8	5.6	4.0	<0.01		29.9	4.5	3.1	0.02
Father's age 35+	36.4	66.1	71.6	<0.01		40.8	60.2	67.4	<0.01
Father Non-Hispan. White	68.1	85.6	87.4	<0.01		71.7	88.2	87.7	0.43
Father Bach Deg. Postgrad	40.5	65.6	69.4	<0.01		44.2	65.6	70.7	<0.01
Father U.S. Born	71.3	81.2	81.9	0.37		74.8	83.6	82.8	0.53
Del. Payer Source Private	58.7	92.0	96.8	<0.01		61.4	93.8	96.2	<0.01
Nulliparous	45.7	39.4	62.4	<0.01		21.7	30.8	31.6	0.08
Gestational Diabetes	5.4	8.3	8.1	0.67		7.9	10.8	9.9	0.36
Other Diabetes	1.1	1.9	2.0	0.64		1.7	2.8	2.4	0.34
Pregnancy-Induced Hypert	8.3	10.2	12.8	<0.01		20.6	26.9	24.7	0.15
Chronic Hypertension	1.6	2.7	3.2	0.07		2.6	3.6	3.0	0.32
Smoked During Pregnancy	7.8	1.8	0.8	<0.01		6.9	0.8	0.8	0.80
Adequate + Prenatal Care	37.6	48.0	48.8	0.01		75.4	82.6	84.8	<0.01

	Singletons				Twins			
	FERTILE	SUBFERTILE – No ART	ART	ART vs Subfertile	FERTILE	SUBFERTILE – No ART	ART	ART vs Subfertile
N (Live births and fetal deaths)	308,103	5,552	6,480	P*	8,645	1,057	4,791	P*
	%	%	%	%	%	%		
Primary cesarean	21.5	29.0	38.6	<0.01	62.9	67.3	75.4	<0.01
Infant Gender Male	51.2	50.5	50.9	0.63	50.5	50.0	51.6	0.33
Any Infertility Condition	2.9	7.2	8.4	0.01	2.9	6.6	9.0	0.01

* p values represent comparison of ART v Subfertile group. ART vs. FERTILE is statistically significantly different in proportion at $p < .01$ in every comparison except for: infant gender for singleton, and chronic hypertension and infant gender for twins

Table 2

Perinatal Outcomes by Maternal Fertility Status and Plurality

	Singleton				Twins			
	FERTILE	SUBFERTILE – No ART	ART	ART vs Subfertile	FERTILE	SUBFERTILE – No ART	ART	ART vs Subfertile
N* (Live Births)	307,320	5,536	6,470	p**	8,569	1,046	4,774	p**
Preterm Birth (%)			<0.01					0.03
<32 completed weeks	0.9	1.1	1.7		9.7	11.6	8.9	
32–33	0.7	1.0	1.4		8.3	9.5	8.3	
34–36	4.8	6.0	7.1		35.0	35.4	36.6	
<i>Total Preterm (<37 weeks)</i>	<i>6.4</i>	<i>8.1</i>	<i>10.2</i>		<i>53.0</i>	<i>56.5</i>	<i>53.8</i>	
37–38 completed weeks	21.7	26.1	25.8		38.4	37.9	39.2	
39–40	60.5	56.5	54.7		8.4	5.7	6.9	
41+	11.5	9.4	9.2		0.3	0.0	0.2	
Gestational Age (mean completed weeks & S.D.)	39.0 (1.8)	38.7 (2.0)	38.6 (2.2)	<0.01	35.5 (3.3)	35.0 (3.9)	35.6 (3.0)	<0.01
Birthweight (%)			<0.01					<0.01
<1,500g	0.8	1.0	1.5		9.1	10.3	7.7	
1500–2499g	4.6	4.7	6.3		43.9	40.2	42.6	
<i>Low Birthweight (<2500 gms)</i>	<i>5.4</i>	<i>5.7</i>	<i>7.8</i>		<i>53.0</i>	<i>50.5</i>	<i>50.3</i>	
2500+ g	94.6	94.3	92.2		47.1	49.5	49.8	
Birthweight (average gms & S.D.)	3362 (552)	3382 (579)	3311 (606)	<0.01	2383 (636)	2369 (692)	2440 (615)	<0.01
Small for Gestational Age (%)	8.1	6.5	8.1	<0.01	20.6	16.9	17.9	0.46
N (live births + fetal deaths)	308,103	5,552	6,480		8,645	1,057	4,791	
Perinatal Death (per 1,000)	4.3	5.8	4.2	0.21	25.7	61.5	11.5	<0.01

* N based on live births for gestational age, birthweight. N for and perinatal death based on live births and fetal deaths.

** All comparisons between ART vs. FERTILE group significant at $p < .01$ except SGA and perinatal deaths among singletons and preterm birth, gestational age among twins. Chi square used for categorical variables; t test for continuous.

Table 3

Risks of Adverse Perinatal Outcomes by Fertility Group and Plurality[^]

Outcome [*]	Singletons						Twins					
		AOR	95% CI	P Value [*]	AOR	95% CI	P Value [*]	AOR	95% CI	P Value [*]	AOR	95% CI
Preterm												
	FERTILE	1.00	(Reference)	----	0.80	(0.72, 0.89)	<0.01	1.00	(Reference)	----	0.74	(0.31, 1.76)
	SUBFERTILE – No ART	1.24	(1.12, 1.38)	<0.01	1.00	(Reference)	----	1.35	(0.57, 3.20)	0.50	1.00	(Reference)
	ART	1.53	(1.40, 1.67)	<0.01	1.23	(1.08, 1.41)	<0.01	0.89	(0.68, 1.18)	0.43	0.66	(0.23, 1.90)
Low Birthweight												
	FERTILE	1.00	(Reference)	----	0.83	(0.74, 0.94)	<0.01	1.00	(Reference)	----	0.99	(0.83, 1.18)
	SUBFERTILE – No ART	1.20	(1.06, 1.36)	<0.01	1.00	(Reference)	----	1.01	(0.85, 1.20)	0.92	1.00	(Reference)
	ART	1.51	(1.37, 1.67)	<0.01	1.26	(1.08, 1.47)	<0.01	0.98	(0.89, 1.09)	0.77	0.98	(0.82, 1.17)
Small-for-Gestation												
	FERTILE	1.00	(Reference)	----	1.05	(0.94, 1.17)	0.39	1.00	(Reference)	----	1.25	(1.02, 1.52)
	SUBFERTILE – No ART	0.95	(0.85, 1.06)	0.39	1.00	(Reference)	----	0.80	(0.66, 0.98)	0.03	1.00	(Reference)
	ART	1.05	(0.96, 1.16)	0.31	1.10	(0.96, 1.27)	0.18	0.85	(0.75, 0.96)	<0.01	1.06	(0.86, 1.30)
Perinatal Death												
	FERTILE	1.00	(Reference)	----	0.66	(0.46, 0.95)	0.03	1.00	(Reference)	----	0.27	(0.17, 0.42)
	SUBFERTILE – No ART	1.51	(1.05, 2.17)	0.03	1.00	(Reference)	----	3.73	(2.37, 5.87)	<0.01	1.00	(Reference)
	ART	1.00	(0.67, 1.50)	0.99	0.66	(0.40, 1.11)	0.12	0.55	(0.34, 0.89)	0.01	0.15	(0.09, 0.25)

* Sample based on live births for gestational age, low birthweight and small for gestational age. Sample for perinatal death based on live births and fetal deaths.

[^] Models adjusted for maternal age, race/ethnicity, marital status, maternal education, payer for delivery, smoking, prenatal care, parity, chronic and pregnancy associated hypertension, other fertility related condition and infant gender