Fertility Treatment Is Associated with Stay in the Neonatal Intensive Care Unit and Respiratory Support in Late Preterm Infants

Erica T. Wang, MD, MAS[1,2], Lauren W. Sundheimer, MD, MS[1,2], Carla Spades, MD[1], Cara Quant, MD[1], Charles F. Simmons, MD[1], and Margareta D. Pisarska, MD[1,2]

Late preterm infants are at risk for short-term morbidities. We report that late preterm singletons conceived with fertility treatment have increased risk for admission to the neonatal intensive care unit and respiratory support compared with spontaneously conceived infants. Fertility treatment may be a risk factor to consider in managing late preterm infants. *(J Pediatr 2017;187:309-12).*

Late preterm births ($34^{0/7}$-$36^{6/7}$ weeks of gestation) account for 7% of all deliveries and more than two-thirds of all preterm births in the United States.[1] The National Institute of Child Health and Human Development sponsored a workshop in 2005 to focus on optimizing the care of late preterm infants,[2] which led to increased awareness of the problems associated with late preterm births.[3] Compared with term infants, late preterm infants are at increased risk for short-term morbidities, including respiratory distress,[4] hypoglycemia,[5] infection,[6] and hyperbilirubinemia.[7] A recent multicenter, randomized trial demonstrated that administration of betamethasone to women at risk for late preterm delivery reduced the risk of neonatal respiratory complications,[8] highlighting the importance of this population and need for changes in practice management. Increased morbidity continues into childhood, with late preterm infants having a higher risk for respiratory diseases such as asthma,[9] neurodevelopment delay, and language disorders.[10,11]

Infants conceived by fertility treatment, including in vitro fertilization (IVF) and non-IVF fertility treatment (NIFT), such as ovulation induction and intrauterine insemination, are at a higher risk for preterm delivery[12-15] and low birth weight[16,17] independent of multiple gestation. One study suggests that IVF conceptions have a 1.5-fold increased risk of preterm delivery between 32 and 36 weeks of gestation.[13] However, there are no studies investigating the outcomes of late preterm infants conceived with fertility treatment compared with spontaneously conceived infants. To address this gap in knowledge, we assessed whether late preterm infants conceived with fertility treatment (IVF or NIFT) are at higher risk for neonatal intensive care unit (NICU) admission and greater respiratory support compared with infants conceived spontaneously.

Methods

A retrospective cohort study was conducted for all singleton gestations delivering between $34^{0/7}$ and $36^{6/7}$ gestational weeks at Cedars-Sinai Medical Center from January 1, 2013, to December 31, 2014. The protocol was approved by the Institutional Review Board. Mode of conception (spontaneous, IVF, or NIFT) was determined based on an extensive chart review of labor floor admission notes and prenatal records, which has been described previously.[18] IVF is the mainstay of assisted reproductive technology and primarily involves the fertilization of oocytes with sperm in the laboratory and subsequent embryo transfer to the uterus. NIFT consists of various other medical interventions that include ovarian stimulation with pharmacologic agents such as selective estrogen receptor modulators, aromatase inhibitors, and gonadotropins, with or without intrauterine insemination. Pregnancies were classified into 2 groups: spontaneous conceptions and fertility treatment (IVF or NIFT) conceptions. The following data were also abstracted: maternal diabetes mellitus, chorioamnionitis, antenatal steroids, administration of magnesium sulfate during delivery, and type of anesthesia used during delivery.

The primary outcome was NICU admission. Secondary neonatal outcomes included need for any respiratory support (supplemental oxygen, nasal continuous positive airway pressure [CPAP], or intermittent mechanical ventilation [IMV]), maximum respiratory support, surfactant administration, infection, hypoglycemia, feeding difficulties, hyperbilirubinemia, and seizures. Over the time period of the study, our NICU implemented guidelines for the admission of late preterm infants, initially for infants delivered between $34^{0/7}$ and $34^{6/7}$ weeks and then subsequently for infants delivered between $35^{0/7}$ and $35^{6/7}$ weeks. Because of these evolutions in admission guidelines, we emphasize the secondary neonatal outcomes to validate NICU admissions and reduce bias. A requirement for supplemental respiratory support would have necessitated NICU admission at our institution. Neonatal outcomes were abstracted from a chart review of NICU discharge

CPAP	Continuous positive airway pressure
IMV	Intermittent mechanical ventilation
IVF	In vitro fertilization
NICU	Neonatal intensive care unit
NIFT	Non-IVF fertility treatment

From the [1]Cedars-Sinai Medical Center; and [2]UCLA David Geffen School of Medicine, Los Angeles, CA

Supported by the National Institutes of Health (R01HD074368 [to M.P.]). The authors declare no conflicts of interest.

Portions of this study were presented as a poster during the American Society for Reproductive Medicine Meeting, Salt Lake City, Utah, October 15-19, 2016.

http://dx.doi.org10.1016/j.jpeds.2017.05.020

summaries and the NICU Database Report, which is generated systematically after each admission.

The Student *t* test, Wilcoxon rank-sum test, and χ^2 test were used to compare maternal characteristics and neonatal outcomes as appropriate. Multivariate logistic regression analyses were then performed to determine the independent association of fertility treatment on NICU admission and secondary neonatal outcomes. The regression model for NICU admission was adjusted for maternal age, parity, and cesarean delivery, 3 potential confounders that were significantly different between the 2 groups on univariate analyses ($P < .05$). The regression model for respiratory support was adjusted for cesarean delivery and male infant sex, both of which are known risk factors for respiratory distress syndrome.[19-21] Data analyses were performed using StataIC (version 13, StataCorp, College Station, Texas).

Results

Of 585 singleton deliveries, there were 523 spontaneous, 47 IVF (8.0%), and 15 NIFT conceptions (2.6%). Women who conceived with fertility treatment were older (38.0 years vs 32.9 years), more likely to be nulliparous (67.7% vs 52%), and deliver by cesarean delivery (67.2% vs 40.3%) compared with women who conceived spontaneously (**Table I**). There were no differences between the 2 groups in terms of maternal diabetes, chorioamnionitis, antenatal steroids, magnesium sulfate, or type of anesthesia used during delivery.

There was no difference in birth weight, gestational age, or size for gestational age, between the 2 groups; however, infants conceived by fertility treatment (IVF or NIFT) demonstrated depressed 1-minute, but not 5-minute, Apgar scores by tertiles (**Table II**). Infants conceived by fertility treatment also had longer overall hospital stays (4.0 days vs 2.9 days; $P = .0008$) and a higher risk of NICU admission (50% vs 28.5%; $P = .001$) (**Table II**). These infants were more likely to require respiratory support (25.8% vs 11.7%; $P = .002$), require more aggressive respiratory support (CPAP 9.7% vs 3.6% [$P = .026$]; IMV 9.7% vs 3.6% [$P = .026$]), and receive surfactant (8.1% vs 2.5% [$P = .016$]) (**Table II**). Infants conceived by fertility treatment were more likely to be diagnosed with hyperbilirubinemia (27.4% vs 12.1% [$P = .001$]), but there were no differences in other diagnoses of infection, hypoglycemia, feeding difficulties, or seizures between the 2 groups (**Table II**).

In multivariate logistic regression analyses adjusted for maternal age, cesarean delivery, and nulliparity, fertility treatment was associated independently with a 2-fold increased odds of NICU admission (OR 2.44; 95% CI 1.36-4.37). In analyses adjusted for cesarean delivery and infant sex, fertility treatment was independently associated with a 2-fold increased odds of supplemental respiratory support (OR 2.16; 95% CI 1.12-4.17), and a 2-fold increased odds of requiring more aggressive respiratory support in the form of either CPAP or IMV (OR 2.41; 95% CI 1.14-5.10). IVF conceptions had both a higher risk of NICU admission (OR 2.08; 95% CI 1.1-4.7) and requiring more aggressive respiratory support (OR 2.53; 95% CI 1.12-5.70) compared with spontaneous conceptions, whereas NIFT conceptions demonstrated an increased risk of NICU

Table I. Maternal characteristics

	Spontaneous (n = 523)	Fertility treatment (n = 62)	*P* value
Maternal age, y*	32.9 (5.4)	38.0 (5.1)	<.001
Maternal race, n (%)†			.12
White	333 (63.9)	47 (75.8)	
African American	67 (12.9)	3 (4.8)	
Asian	90 (17.3)	7 (11.9)	
Other	31 (6.0)	5 (8.1)	
Nulliparous, n (%)	272 (52.0)	42 (67.7)	.02
Maternal diabetes, n (%)	62 (11.9)	5 (8.1)	.376
Chorioamnionitis, n (%)	12 (2.3)	0	.228
Antenatal steroids, n (%)	71 (13.6)	11 (17.7)	.372
Magnesium sulfate, n (%)	89 (17.0)	13 (21.0)	.438
Anesthesia, n (%)‡			.157
None/local	46 (8.5)	3 (5.0)	
Epidural/spinal	459 (89.3)	54 (90.0)	
General	9 (1.8)	3 (5.0)	
Cesarean delivery, n (%)	209 (40.3)	41 (67.2)	<.001
Gestational age, wk	35.9 (0.81)	35.8 (0.79)	.80
Completed gestational weeks, n (%)			.725
34	79 (15.1)	11 (17.7)	
35	149 (28.5)	15 (24.2)	
36	295 (56.4)	36 (56.6)	

*Continuous variables are represented as mean (standard deviation). *P* values derived by Student *t* test.
†Categorical variables are represented as frequency (proportion). *P* values derived by χ^2 test.
‡Data available for 574 observations.

Table II. Neonatal outcomes

	Spontaneous (n = 523)	Fertility treatment (n = 62)	*P* value
Female sex, n (%)*	226 (43.3)	32 (51.6)	.21
Birth weight, g†	2597 (584)	2570 (649)	.73
Size for gestational age, n (%)‡			.78
Appropriate	344 (80.6)	39 (84.8)	
Large	15 (3.5)	1 (2.2)	
Small	68 (15.9)	6 (13.0)	
1-Minute Apgar, n (%)			.02
0-3	11 (2.1)	5 (8.1)	
4-6	49 (9.5)	8 (12.9)	
7-10	456 (88.4)	49 (79.0)	
5-Minute Apgar, n (%)			.37
0-3	2 (0.4)	1 (1.6)	
4-6	11 (2.1)	2 (3.3)	
7-10	505 (97.5)	58 (95.1)	
Length of hospital stay, d§	2.9 (2.1-4.6)	4.0 (2.9-6.5)	.0008
NICU admission, n (%)‡	149 (28.5)	31 (50)	.001
Any respiratory support, n (%)	61 (11.7)	16 (25.8)	.002
Maximum respiratory support, n (%)			
Supplemental O_2	23 (4.4)	4 (6.5)	.466
CPAP	19 (3.6)	6 (9.7)	.026
IMV	19 (3.6)	6 (9.7)	.026
Surfactant, n (%)	13 (2.5)	5 (8.1)	.016
Infection, n (%)	6 (1.2)	0	.40
Hypoglycemia, n (%)	16 (3.1)	3 (4.8)	.46
Feeding difficulties, n (%)	25 (4.8)	1 (1.6)	.25
Hyperbilirubinemia, n (%)	63 (12.1)	17 (27.4)	.001
Seizures, n (%)	2 (0.3)	0	.63

*Categorical variables are represented as frequency (proportion). *P* values derived by χ^2 test.
†Continuous variables are represented as mean (standard deviation) unless otherwise specified. *P* values derived by Student *t* test.
‡Data available for 473 observations.
§Data represented as median (IQR). *P* value derived by Wilcoxon rank-sum test.