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Fertility Treatment Is Associated With NICU Stay and Respiratory Support In Late Preterm Infants

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Abstract

Late preterm infants are at risk for short term morbidities. We find that late preterm singletons conceived with fertility treatment have an increased risk for NICU admission and respiratory support compared to spontaneously conceived infants. Fertility treatment may be a risk factor to consider in managing late preterm infants.

Keywords

in vitro fertilization; assisted reproductive technology

Introduction

Late preterm births (34 0/7 to 36 6/7 weeks of gestation) account for 7% of all deliveries and over 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 to term infants, late preterm infants are at increased risk for short term morbidities, including respiratory distress (4), hypoglycemia (5), infection (6), and hyperbilirubinemia (7). Most recently, a multicenter, randomized trial demonstrated that administration of betamethasone to women at risk for late preterm delivery significantly reduced the risk of neonatal respiratory complications (8), bringing to the forefront the importance of this cohort and changes in practice management. Increased morbidity continues into childhood, with late preterm infants having a higher risk for respiratory disease notably asthma (9) and neurodevelopment delay and language disorders (10, 11).

We know that infants conceived by fertility treatment, encompassing both in vitro fertilization (IVF) and non-IVF fertility treatment (NIFT) such as ovulation induction and

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intrauterine insemination, are at a higher risk for preterm delivery (12-15) and low birth weight (16, 17) independent of multiple gestations. One study suggests that IVF conceptions have a 1.5x increased risk of preterm delivery between 32-36 weeks gestation (13). However, there are no studies investigating the outcomes of late preterm infants conceived with fertility treatment compared to spontaneously conceived infants. To address this gap in knowledge, our study is designed to assess whether late preterm infants conceived with fertility treatment (IVF or NIFT) are at a higher risk for neonatal intensive care unit (NICU) admission and greater respiratory support compared to spontaneously conceived infants.

Methods

A retrospective cohort study was conducted for all singleton gestations delivering between 34 0/7 to 36 6/7 gestational weeks at Cedars-Sinai Medical Center from January 1, 2013 to December 31, 2014 under an Institutional Review Board-approved protocol (Pro00031384). 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 previously described (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. Conceptions were classified into two 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 – 34 6/7 weeks and then subsequently for infants delivered between 35 0/7 – 35 6/7 weeks. Because of the ongoing evolution 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 summaries and the NICU Database Report which is systematically generated after each admission.

Standard descriptive statistics for univariate analysis, including students t-test, Wilcoxon ranksum test, and Chi-square 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, three potential confounders which were significantly different between the two groups in univariate analyses ($P<0.05$). 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).

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 v. 32.9 years), more likely to be nulliparous (67.7% v. 52%), and deliver by cesarean delivery (67.2% v. 40.3%) compared to women who conceived spontaneously (Table 1). There were no differences between the two groups in terms of maternal diabetes, chorioamnionitis, antenatal steroids, magnesium sulfate, or type of anesthesia used during delivery.

In univariate analyses of neonatal outcomes, there was no difference in birth weight or gestational age, or size for gestational age, between the two groups; however, infants conceived by fertility treatment (IVF or NIFT) demonstrated depressed 1 minute, but not 5 minute, Apgar scores by tertiles (Table 2). Infants conceived by fertility treatment also had and a longer overall hospital stay (4.0 days v. 2.9 days, P=0.0008) a significantly higher risk of NICU admission (50% v. 28.5%, P=0.001) (Table 2). These infants were more likely to require respiratory support (25.8% v. 11.7%, P=0.002), require more aggressive respiratory support (CPAP 9.7% v. 3.6%, P=0.026, IMV 9.7% v. 3.6%, P=0.026), and receive surfactant indicative of true respiratory distress syndrome (8.1% v. 2.5%, P=0.016) (Table 2). Infants conceived by fertility treatment were also more likely to be diagnosed with hyperbilirubinemia (27.4% v. 12.1%, P=0.001), but there were no differences in other diagnoses of infection, hypoglycemia, feeding difficulties, or seizures between the two groups (Table 2).

In multivariate logistic regression analyses adjusted for maternal age, cesarean delivery, and nulliparity, fertility treatment was independently associated with a two-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 two-fold increased odds of supplemental respiratory support (OR 2.16, 95% CI 1.12-4.17), and a two-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 to spontaneous conceptions, while NIFT conceptions demonstrated an increased risk of NICU admission (OR 3.70, 95% CI 1.3-10.7). When analyses were stratified for male infants and female infants, fertility treatment was associated with increased odds for supplemental respiratory support for male infants (OR 2.73, 95% CI 1.16-6.45), but not female infants (OR 1.59, 95% CI 0.56-4.48).

Discussion

In this retrospective cohort study, we determined that late preterm infants conceived with fertility treatment (IVF or NIFT) had a two-fold increased odds of NICU admission compared to spontaneously conceived infants after accounting for potential confounders

including maternal age, cesarean delivery, and nulliparity. Furthermore, upon NICU admission, fertility treatment was an independent predictor of future supplemental respiratory support and a higher level of maximum respiratory support such as CPAP, IMV, or surfactant replacement therapy.

Although we know that IVF singletons are at a greater risk of adverse perinatal outcomes, this is the first study to our knowledge focusing on late preterm outcomes of both IVF and NIFT treatments. Although prior studies have focused primarily on the outcomes of early preterm and extreme prematurity (12, 16), it is notable that late preterm infants, not limited to singletons, make up the majority of preterm births and contribute significantly to the staggering $26 billion in annual US healthcare expense (22). One of the major strengths of our study is that our primary outcome of NICU admission was supported by therapeutic intensity of respiratory support. We examined multiple levels of respiratory support, all of which would require admission to the NICU and thereby eliminating bias in NICU admission.

It is unclear what causal pathways result in excess respiratory morbidity in late preterm IVF or NIFT infants compared with spontaneously conceived infants. Ultimately, it remains to be determined whether it is the fertility treatment and/or the underlying infertility that contributes to adverse outcomes. Although some studies have concluded that pregnancies conceived with fertility treatment are comparable to spontaneous conceptions in terms of cytogenetic abnormalities (23, 24), other studies have identified an increased risk of birth defects (25-27) associated with fertility treatment. The developmental origin of health and disease hypothesis suggests that there are specific windows of sensitivity during fetal development in which environmental exposures can reprogram the genome and predispose to disease later in life (28). The preimplantation state is particularly sensitive to epigenetic regulation and animal models have shown that IVF and embryo culture generate imprinting errors by inducing abnormal DNA and histone methylation marks, as well as abnormal global patterns of gene expression (29, 30). Thus, one speculation is that the fertility treatment itself is a risk factor for future neonatal and respiratory disease, though further studies are needed to substantiate this.

Our study confirms an increased risk of cesarean delivery for singleton gestations associated with fertility treatment. Maternal age is a known risk factor for cesarean delivery, and we have previously demonstrated no difference in indication for cesarean delivery between spontaneous conceptions and IVF conceptions (31). Male infant sex and cesarean delivery are significant risk factors for respiratory distress syndrome for all gestational ages (19-21) and our study supports these associations. Although our study concludes that fertility treatment is a predictor of supplemental respiratory support independent of cesarean delivery, clinicians should aim to decrease cesarean delivery rates in this high risk population to improve neonatal outcomes.

Another finding of our study was the increase risk of hyperbilirubinemia in infants conceived after fertility treatment compared to infants conceived spontaneously. Maternal age and cesarean delivery are risk factors associated with hyperbilirubinemia (32, 33), as well as fertility treatment conceptions which may in part explain our finding.

An additional strength of this study is improved ascertainment of mode of conception and neonatal outcomes based upon chart review, instead of relying only on diagnostic codes. For example, a discharge code of respiratory distress syndrome may subsume several distinct diagnoses. Our alternative approach utilized objective respiratory therapy intensity categories, such as CPAP or IMV, to support our outcomes analysis.

We acknowledge that this study is limited as it is a single institution retrospective study. This study focuses on singletons only and may not apply to multiple gestations, which accounts for a large proportion of premature infants conceived by fertility treatment; however we view this as a strength as multiple births are a significant confounder in evaluating neonatal outcomes (34). It should be noted that the two statistically significant secondary neonatal outcomes – respiratory distress and hyperbilirubinemia – were also the outcomes with the highest baseline incidence. We may see further differences with a multi-center prospective study to allow for a larger sample size and greater number of less common morbidities.

In conclusion, in this retrospective study of late preterm infants, fertility treatment was an independent risk factor for NICU admission and increased respiratory support. Future studies may focus on the differential effect of IVF compared to NIFT, as well as multifetal pregnancies. Larger, prospective studies are needed to verify and expand our findings and to determine whether fertility treatment should be a risk factor to consider in the management of late preterm infants.

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Abbreviations

IVF
in vitro fertilization

NIFT
non-IVF fertility treatment

NICU
neonatal intensive care unit

continuous positive airway pressure
CPAP

intermittent mechanical ventilation
IMV

Table 1

Maternal Characteristics

	Spontaneous N=523	Fertility Treatment N=62	P-value
Maternal Age, y[1]	32.9 (5.4)	38.0 (5.1)	<0.001
Maternal Race, n(%)[2]			0.12
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)	0.02
Maternal Diabetes, n(%)	62 (11.9)	5 (8.1)	0.376
Chorioamnionitis, n(%)	12 (2.3)	0	0.228
Antenatal steroids, n(%)	71 (13.6)	11 (17.7)	0.372
Magnesium Sulfate, n(%)	89 (17.0)	13 (21.0)	0.438
Anesthesia, n(%)[3]			0.157
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)	<0.001
Gestational age, weeks	35.9 (0.81)	35.8 (0.79)	0.80
Completed gestational weeks, n(%)			0.725
34	79 (15.1)	11 (17.7)	
35	149 (28.5)	15 (24.2)	
36	295 (56.4)	36 (56.6)	

[1] Continuous variables are represented as mean (standard deviation). P-values derived by student t-test.

[2] Categorical variables are represented as frequency (proportion). P-values derived by Chi-square test.

[3] Data available for 574 observations.

Table 2

Neonatal Outcomes

	Spontaneous N=523	Fertility Treatment N=62	P-value
Female sex, n(%)[1]	226 (43.3)	32 (51.6)	0.21
Birth weight, grams[2]	2597 (584)	2570 (649)	0.73
Size for Gestational Age, n(%)[3]			0.78
Appropriate for Gestational Age	344 (80.6)	39 (84.8)	
Large for Gestational Age	15 (3.5)	1 (2.2)	
Small for Gestational Age	68 (15.9)	6 (13.0)	
1 minute Apgar, n(%)			0.02
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(%)			0.37
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, days[4]	2.9 (2.1-4.6)	4.0 (2.9-6.5)	0.0008
NICU admission, n(%)[3]	149 (28.5)	31 (50)	0.001
Any Respiratory Support, n(%)	61 (11.7)	16 (25.8)	0.002
Maximum Respiratory Support, n(%)			
Supplemental O2	23 (4.4)	4 (6.5)	0.466
CPAP	19 (3.6)	6 (9.7)	0.026
IMV	19 (3.6)	6 (9.7)	0.026
Surfactant, n(%)	13 (2.5)	5 (8.1)	0.016
Infection, n(%)	6 (1.2)	0	0.40
Hypoglycemia, n(%)	16 (3.1)	3 (4.8)	0.46
Feeding difficulties, n(%)	25 (4.8)	1 (1.6)	0.25
Hyperbilirubinemia, n(%)	63 (12.1)	17 (27.4)	0.001
Seizures, n (%)	2 (0.3)	0	0.63

[1] Categorical variables are represented as frequency (proportion). P-values derived by Chi-square test.

[2] Continuous variables are represented as mean (standard deviation) unless otherwise specified.P-values derived by student t-test.

[3] Data available for 473 observations.

[4] Data represented as median (interquartile range). P-value derived by Wilcoxon ranksum test.