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Maternal and Neonatal Outcomes Associated with Infertility

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Abstract

Objective: To investigate perinatal outcomes in a cohort of fertile and infertile nulliparous women.

Design: Retrospective cohort study

Setting: Academic medical center

Patients: All nulliparous women delivering singletons ≥24 weeks gestation at our center from January 1- December 31, 2012 were included. Women were classified into two groups – fertile and infertile – based on a chart review at the time of delivery.

Outcome Measure: Perinatal outcomes of interest included mode of delivery, gestational age at delivery, and birth weight.

Results: A total of 3293 mother/infant dyads fulfilled the inclusion criteria. Of these, 277 women(8.4%) were classified as infertile. Infertile women were significantly older than fertile women. In bivariate analyses, infertile women were more likely to undergo cesarean delivery (51.8% vs. 36.1%, P<0.001) and deliver at an earlier gestational age (38.9±2.3 vs. 39.4±1.7 weeks, P<0.0001). Infertility was no longer significantly associated with cesarean delivery after adjusting for maternal age. Infertility remained associated with an earlier gestational age at delivery after adjusting for maternal age and maternal race (β coefficient −0.42, 95% CI −0.64, −0.2). There was

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no difference in infant birth weight. Late preterm deliveries (34 – 36 completed gestational weeks) accounted for 8.3% of deliveries for infertile women compared to 4.3% for fertile women (P=0.032).

Conclusions: We conclude that the increased risk of cesarean section associated with infertility is driven by maternal age. Late preterm infants represent a key cohort for further evaluation in the perinatal outcomes of infertile women.

Keywords

infertility; IVF; assisted reproductive technology; preterm births

Introduction

Approximately 15% of couples experience infertility and fertility treatments are on the rise, with *in vitro* fertilization (IVF) contributing to 1.5% of live births in the United States and non-IVF fertility treatment (NIFT) contributing 4.6[1,2]. NIFT includes ovulation induction agents such as clomiphene citrate, letrozole, gonadotropin hormone injections, and/or intrauterine inseminations. Multiple studies have focused primarily on IVF perinatal outcomes such as preterm delivery[3], low birth weight[4–6], and congenital defects[7–10]. Fewer studies have examined non-IVF treatment (NIFT) conceptions. A recent study demonstrated that in singletons, any fertility treatment including IVF, ovarian stimulation, and intrauterine insemination, was associated with preterm birth and low birth weight compared to women who did not use any fertility treatment[11].

Although prematurity accounts for 12% of all births, over 36% of IVF infants and approximately 12% of NIFT conceptions are born premature[12,13]. More recently, the Institute of Medicine (US) Committee on Understanding Premature Birth coined the term “late preterm” for infants delivered between 34 and 36 6/7 weeks gestation [14]. Late preterm infants make up nearly 75% of all preterm births[15] and 20% to 25% of NICU admissions in the United States. Compared to full-term infants, late preterm infants are at increased risk for neonatal mortality and morbidity [14,16–18], and morbidity continues into childhood development[19–22]. The contribution of IVF/NIFT to late preterm births relative to early preterm births is not known.

In this study, we aim to investigate perinatal outcomes in a cohort of fertile and infertile nulliparous women at our center over a one year time period.

Materials and Methods

In this IRB-approved retrospective cohort study (Pro00031384), we reviewed the charts of all nulliparous women delivering singletons ≥24 weeks gestation at Cedars-Sinai Medical Center from January 1, 2012 through December 31, 2012. Data from the electronic medical records were abstracted for documentation of infertility and fertility treatment by extensive review of prenatal records, hospital admission notes, discharge summaries, and genetic counseling notes. This abstraction process has been described previously[23]. Fertility treatments were classified as IVF or NIFT, such as clomiphene citrate, gonadotropin

injections, or intrauterine inseminations. The scanned prenatal record was found to be the most common source for infertility diagnosis and fertility treatment information at our institution. Preconception and prenatal care records, including genetic counseling notes and actual fertility treatment processes, were available in the electronic medical records for only a subset of patients (<50%). We did not review treatment records from outside fertility clinics. Patients were classified as infertile if the chart had provider documentation of infertility and/or use of fertility treatment. All remaining patients were classified as fertile. Data was also abstracted for socio-demographic variables, mode of delivery, gestational age at delivery, and infant birth weight.

Standard descriptive statistics were utilized to compare baseline characteristics between the infertile and fertile group. Multivariate regression models were performed to determine the independent association of infertility with outcomes of cesarean delivery and gestational age at delivery. A subset analysis of late preterm infants, delivered between 34 and 36 completed gestational weeks, was conducted. Indication for late preterm delivery was classified as 1) labor or rupture of membranes, 2) maternal indications, including hypertensive disorders (ie. preeclampsia) and placentation disorders (ie. placenta previa), and 3) fetal indications, including intrauterine growth restriction and non-reassuring fetal testing (ie. by fetal heart monitor or oligohydramnios). We also performed a sensitivity analysis to include only infertile patients who conceived with fertility treatment and fertile patients who conceived spontaneously. All analyses were performed using Stata IC 13.1 (College Station, Texas).

Results

A total of 3293 mother/infant dyads fulfilled the inclusion criteria. Of these, 277 women (8.4%) were classified as infertile. Infertile women were significantly older than fertile patients (37.4±5.3 vs. 31.5±5.3 years, P<0.0001) (Table 1). Of the infertile women, 68 (24.5%) did not have documented fertility treatment, and may represent cases of subfertility. Of the fertile patients, 8 (0.26%) had documented fertility treatment, and may represent cases in which fertility treatment was not performed for infertility (ie. IVF for single gene defects or donor inseminations). In bivariate analyses, infertile patients had a higher prevalence of cesarean delivery (51.8% vs. 36.1%, P<0.001), and also delivered at an earlier gestational age (38.9±2.3 vs. 39.4±1.7 weeks, P<0.0001). There was no difference in infant birth weight.

In multivariate logistic regression analyses, infertility was no longer significantly associated with cesarean delivery after adjusting for maternal age, maternal race, and gestational age at delivery (Odds Ratio 1.24, 95% CI 0.95–1.62).

In multivariate linear regression analyses, infertility remained associated with an earlier gestational age at delivery after adjusting for maternal age and maternal race (β coefficient −0.42, 95% CI −0.64, −0.2). To further explore this, we compared the prevalence of preterm, late preterm, early term, and term deliveries between infertile and fertile women (Table 2). Preterm deliveries (<34 completed gestational weeks) accounted for 2.9% of deliveries for infertile women compared to 1.3% for fertile women (P=0.032), while late preterm deliveries (34 – 36 completed gestational weeks) accounted for 8.3% of deliveries for

infertile women compared to 4.3% for fertile women (P=0.003) (Table 2). Of the 200 preterm and late preterm infants, indication for delivery (rupture of membranes/labor, maternal indications, or fetal indications) did not differ between infertile and fertile women (P=0.28).

In a sensitivity analysis that included only infertile patients who conceived with fertility treatment and fertile patients who conceived spontaneously, our results were unchanged.

Discussion

Our study demonstrates that women with a history of infertility are more likely to undergo cesarean delivery due to maternal age and deliver at an earlier gestational age. More notably, women with infertility are more likely to deliver a late preterm infant than women without documented infertility. This is the first study to focus on the contribution of infertility on late preterm births, and carries significant implications given the possible neonatal and childhood morbidities associated with late preterm infants.

The association between infertility and cesarean delivery is not surprising as the association is driven primarily by maternal age and the association is no longer significant after adjusting for maternal age[24]. We previously showed that among very advanced maternal age pregnancies, those who conceive by IVF had a two-fold increased risk of primary cesarean delivery compared to those who conceive spontaneously[25]. Indications for cesarean delivery included non-reassuring fetal heart rate, failure to progress, and elective procedure. Further studies are needed to guide counseling in older women, independent of fertility status, regarding the factors which contribute to an increased risk of cesarean delivery. One of the strengths of this study is that it is from a single institution, resulting in less potential for bias based on practice patterns due to geographical differences.

Prior studies suggest that IVF pregnancies, even singletons, are associated with low birthweight and preterm deliveries[4,26,27]. However, to our knowledge, our findings are among the first to highlight that the majority of preterm births in infertile women are categorized as late preterm. Interestingly, our study did not show a difference in birth weight, contrary to some prior studies. This may be due to a limited sample size. However, our study supports a recent larger study of 93,443 singleton IVF births reported to the Society for Assisted Reproductive Technologies which demonstrated that birth weight percentiles per completed week of gestation for IVF singletons and the general population are comparable in the third trimester[28]. The effect of infertility and/or fertility treatment on early development remains to be determined. Although studies on late preterm infants suggest that they are at increased risk for neonatal mortality and morbidity[14,16–18], it is unknown whether infertility adds a synergistic effect. A recent prospective cohort study concluded that children's development through age 3 years was comparable regardless of infertility or infertility treatment[29].

A limitation of this study is the possible misclassification of infertile and fertile women as not all fertility treatments are uniformly documented by providers. This underscores the urgent need for improved documentation on fertility and details of fertility treatment on a

national level. Existing methods such as reporting fertility treatment on birth certificates in certain states are inadequate, with some studies demonstrating that the sensitivity of reporting IVF was only 27%.[28] We attempted to address the issue of misclassification by performing an sensitivity analysis on infertile patients who conceived with treatment and fertile patients who conceived spontaneously, and we obtained consistent results.

We conclude that the increased risk of cesarean section associated with infertility is driven by maternal age. We also conclude that late preterm infants represent a key cohort for further evaluation in the perinatal outcomes of infertile women.

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References

1. Schieve LA, Devine O, Boyle CA, et al.: Estimation of the contribution of non-assisted reproductive technology ovulation stimulation fertility treatments to US singleton and multiple births. Am J Epidemiol 170:1396–407, 2009 [PubMed: 19854803]
2. Sunderam S, Kissin DM, Crawford SB, et al.: Assisted reproductive technology surveillance -United States, 2011. MMWR Surveill Summ 63:1–28, 2014
3. Wisborg K, Ingerslev HJ, Henriksen TB: In vitro fertilization and preterm delivery, low birthweight, and admission to the neonatal intensive care unit: a prospective follow-up study. Fertil Steril 94:2102–6, 2010 [PubMed: 20188361]
4. Schieve LA, Meikle SF, Ferre C, et al.: Low and very low birth weight in infants conceived withuse of assisted reproductive technology. N Engl J Med 346:731–7, 2002 [PubMed: 11882728]
5. Henningsen AK, Loft A, Malchau SS, et al.: [The prognosis for children born after assisted reproduction]. Ugeskr Laeger 174:2462–6, 2012 [PubMed: 23050688]
6. Kalra SK, Ratcliffe SJ, Coutifaris C, et al.: Ovarian stimulation and low birth weight in newborns conceived through in vitro fertilization. Obstet Gynecol 118:863–71, 2011 [PubMed: 21934450]
7. Davies MJ, Moore VM, Willson KJ, et al.: Reproductive technologies and the risk of birth defects.N Engl J Med 366:1803–13, 2012 [PubMed: 22559061]
8. Hansen M, Kurinczuk JJ, de Klerk N, et al.: Assisted reproductive technology and major birthdefects in Western Australia. Obstet Gynecol 120:852–63, 2012 [PubMed: 22996103]
9. Klemetti R, Gissler M, Sevon T, et al.: Children born after assisted fertilization have an increasedrate of major congenital anomalies. Fertil Steril 84:1300–7, 2005 [PubMed: 16275218]
10. Silver RI, Rodriguez R, Chang TS, et al.: In vitro fertilization is associated with an increased risk of hypospadias. J Urol 161:1954–7, 1999 [PubMed: 10332480]
11. Stanford JB, Simonsen SE, Baksh L: Fertility treatments and adverse perinatal outcomes in a population-based sampling of births in Florida, Maryland, and Utah: a cross-sectional study. BJOG, 2015
12. Sunderam S, Kissin DM, Crawford S, et al.: Assisted reproductive technology surveillance -United States, 2010. MMWR Surveill Summ 62:1–24, 2013
13. Klemetti R, Sevon T, Gissler M, et al.: Health of children born after ovulation induction. FertilSteril 93:1157–68, 2010
14. Raju TN, Higgins RD, Stark AR, et al.: Optimizing care and outcome for late-preterm (near-term) infants: a summary of the workshop sponsored by the National Institute of Child Health and Human Development. Pediatrics 118:1207–14, 2006 [PubMed: 16951017]
15. Woythaler M, McCormick MC, Mao WY, et al.: Late Preterm Infants and Neurodevelopmental Outcomes at Kindergarten. Pediatrics, 2015

16. Shapiro-Mendoza CK, Tomashek KM, Kotelchuck M, et al.: Effect of late-preterm birth and maternal medical conditions on newborn morbidity risk. Pediatrics 121:e223–32, 2008 [PubMed: 18245397]
17. Wang ML, Dorer DJ, Fleming MP, et al.: Clinical outcomes of near-term infants. Pediatrics114:372–6, 2004 [PubMed: 15286219]
18. Escobar GJ, Clark RH, Greene JD: Short-term outcomes of infants born at 35 and 36 weeks gestation: we need to ask more questions. Semin Perinatol 30:28–33, 2006 [PubMed: 16549211]
19. Machado Junior LC, Passini Junior R, Rodrigues Machado Rosa I: Late prematurity: a systematic review. J Pediatr (Rio J) 90:221–31, 2014 [PubMed: 24508009]
20. Rabie NZ, Bird TM, Magann EF, et al.: ADHD and developmental speech/language disordersin late preterm, early term and term infants. J Perinatol 35:660–4, 2015 [PubMed: 25836321]
21. Raby BA, Celedon JC, Litonjua AA, et al.: Low-normal gestational age as a predictor of asthmaat 6 years of age. Pediatrics 114:e327–32, 2004 [PubMed: 15342893]
22. Woythaler MA, McCormick MC, Smith VC: Late preterm infants have worse 24-monthneurodevelopmental outcomes than term infants. Pediatrics 127:e622–9, 2011 [PubMed: 21321024]
23. Wang ET, Ozimek JA, Greene N, et al.: The impact of fertility treatment on severe maternal morbidity. Fertil Steril, 2016
24. Kenny LC, Lavender T, McNamee R, et al.: Advanced maternal age and adverse pregnancy outcome: evidence from a large contemporary cohort. PLoS One 8:e56583, 2013 [PubMed: 23437176]
25. Jackson S, Hong C, Wang ET, et al.: Pregnancy outcomes in very advanced maternal age pregnancies: the impact of assisted reproductive technology. Fertil Steril 103:76–80, 2015 [PubMed: 25450294]
26. Jackson RA, Gibson KA, Wu YW, et al.: Perinatal outcomes in singletons following in vitro fertilization: a meta-analysis. Obstet Gynecol 103:551–63, 2004 [PubMed: 14990421]
27. McGovern PG, Llorens AJ, Skurnick JH, et al.: Increased risk of preterm birth in singleton pregnancies resulting from in vitro fertilization-embryo transfer or gamete intrafallopian transfer: a meta-analysis. Fertil Steril 82:1514–20, 2004 [PubMed: 15589852]
28. Dickey RP, Xiong X, Pridjian G, et al.: Singleton birthweight by gestational age following invitro fertilization in the United States. Am J Obstet Gynecol 214:101 e1–101 e13, 2016
29. Yeung EH, Sundaram R, Bell EM, et al.: Examining Infertility Treatment and Early Childhood Development in the Upstate KIDS Study. JAMA Pediatr:1–9, 2016

Table 1

Baseline characteristics

	Infertile N=277	Fertile N=3016	P-value
Maternal Age, years	37.4±5.3	31.5±5.3	<0.0001
Maternal Race, n(%)			0.023
White	193 (69.9)	2066 (68.8)	
Black- or African-American	16 (15.8)	287 (9.6)	
Asian or Asian-American	49 (17.8)	391 (13.0)	
Other	18 (6.5)	260 (8.7)	
BMI, kg/m^2	23.3±4.6	23.0±4.6	0.3211
Mode of Conception, n(%)			<0.0001
IVF	136 (49.1)	4 (0.13)	
NIFT	73 (26.4)	4 (0.13)	
Presumed Spontaneous	68 (24.5)	3008 (99.7)	
Cesarean Delivery, n(%)	142 (51.8)	1078 (36.1)	<0.001
Gestational age, weeks	38.9±2.3	39.4±1.7	<0.0001
Birth weight, grams[c]	3268±634	3317±510	0.1378

Table 2

Infertility and Gestational Age at Delivery

	Infertile N=277	Fertile N=3016	P value
<34 weeks	8 (2.9)	39 (1.3)	0.032[1]
34– 36 6/7 weeks	23 (8.3)	130 (4.3)	0.003[2]
37–38 6/7 weeks	58 (20.9)	536 (17.8)	0.19[3]
≥39 weeks	188 (67.9)	2311(76.6)	0.001[4]

[1]Chi square test compares deliveries <34 weeks to all deliveries ≥ 34 weeks between infertile and fertile women

[2]Chi square test compares deliveries 34 – 36 6/7 weeks to all other deliveries between infertile and fertile women

[3]Chi square test compares deliveries 37 – 38 6/7 weeks to all other deliveries between infertile and fertile women

[4]Chi square test compares deliveries ≥39 weeks to all other deliveries between infertile and fertile women