Original Article

Trends and Clinical Features of Neonates Conceived via Infertility Treatment：11-year Study in the Perinatal Center at Jichi Medical University Hospital

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Abstract

Background：Infertility treatments（IFT）have been employed for couples having difficulty conceiving. Previous studies indicated that IFT result in the increased rates of the following conditions：multiple pregnancy, low-birth weight infants, preterm delivery, fetal growth restriction（FGR）, and congenital anomalies. All these conditions increase infant morbidity. However, there are few studies examined the data from a single large neonatal intensive care unit（NICU）over a significant time period.

Objectives：We attempt to determine the impact of IFT on NICU practice. We retrieved all data of 3,913 infants admitted to Jichi Medical University Hospital NICU for 11 years, then assessed the clinical features and various morbidities of infants.

Results：Infants from IFT were approximately 10% of all admissions to NICU. We found a considerable amount of FGR in singletons from IFT, as well as CS, in pregnancies following IFT.

Conclusion：There are increasing numbers of infants from IFT, and perinatal intensive care is indispensable for them.

（Key words：infertility treatments, ART, NICU, twins, LBW）

Introduction

For the past 50 years, infertility treatments（IFTs）such as assisted ovulation and artificial insemination have been employed for couples having difficulty conceiving. More recently, assisted reproductive technology（ART）has become commonplace, accounting for almost 2% of all births worldwide including Japan[1, 2]. Advances in IFT, including ART and non-ART IFT, has led to a marked change in clinical practice of the neonatal intensive care unit（NICU）. For example, some studies have reported that IFT increased the rates of the following conditions：multiple pregnancy[3, 4], low birth weight（LBW）infants, preterm delivery[5, 6], fetal growth restriction, and congenital anomalies[5, 7, 8]. All these conditions obviously increase infant morbidity; thus, overtaxing the limited number of beds available in the NICU[9]. The advances in IFT have definitely impacted NICU practice[5]；however, the data from a single large NICU center over a significant time period has not been presented.

In this study, we attempted to determine how IFT has impacted NICU practice. We determined how care has evolved during this time span; we assessed the general clinical features of infants admitted to the NICU, twin gestations, and various infant morbidities, especially LBW infants, fetal growth restriction, and congenital anomalies. We reviewed all data regarding infants admitted to Jichi Medical University（JMU）Hospital NICU during an 11yearperiod：JMU NICU has been caring for approximately 400 infants annually, which represents almost half of the high-risk infants born in Tochigi prefecture, Japan.

Materials and Methods

From January 1997 through December 2007, 3,913 infants were admitted to JMU NICU. These infants were divided into three groups based on type of conception：spontaneous

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(conceived spontaneously), non-ART (conceived with assisted ovulation or artificial insemination), or ART. The ART group included gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), in vitro fertilization-embryo transfer (IVF-ET), in vitro fertilization-blastocyst transfer (IVF-BT), intracytoplasmic sperm injection (ICSI), and use of cryopreserved embryos.

Via medical records, we reviewed perinatal data : mode of conception, number of fetuses, gestational age at delivery, delivery mode, maternal past illnesses, and placental pathology; neonatal data were also reviewed : date of birth, sex, birth weight, congenital anomalies, short-term complications, and cause of death. All data were gathered without patient identification. Fetal growth restriction (FGR) was defined as birth weight less than the 10th percentile of the neonatal growth curve of Japanese infants at birth[10]. Chorionicity was determined by ultrasound performed at early pregnancy and placental pathology after birth. Twin to twin transfusion syndrome (TTTS) was defined by the presence of both severe oligohydramnios in the donor and polyhydramnios in the recipient[11]. A birth weight discordance of more than 25% was defined as birth weight discordancy in twin pregnancies. Maternal past illnesses included chronic hypertension, heart disease, thyroid disease (hyperthyroidism and hypothyroidism), lupus, asthma, psychiatric disorders, neurologic disease, and diabetes mellitus. Congenital anomalies of infants included chromosomal abnormalities, cardiovascular disease, genitourinary anomalies, neurological disease, gastrointestinal disease, orthopedic and plastic surgical disease, and other conditions.

First, perinatal and neonatal data were compared among the three groups. Next, we divided the study period into three intervals (1997-1999, 2000-2003, and 2004-2007) and compared the number of admissions to the NICU, rate of singleton births, and rate of multiple pregnancies in each group among the three periods. Neonatal morbidity was also investigated. Finally, neonatal morbidity and mortality were compared between monochorionic diamniotic (MD) and dichorionic diamniotic (DD) twins. Continuous data were compared between groups by one-fracture analysis of variance (ANOVA). Categorical data were compared using chi-squared test followed by Bonferroni's method to determine between groups differences. All data analyses were performed using SPSS 17.0 stastical package (Chicago, IL, USA). A P value < 0.05 was considered significant.

Results

Table 1 presents the percentage and number of singleton, twin, and triplet births, as well as the clinical characteristics of each group. The rates of singletons, twins, and triplets were significantly different among the groups ($P < 0.001$). CS rate was significantly highest in the ART group (Bonferroni's method, $P < 0.01$). Rate of maternal past illnesses was significantly highest in the spontaneous group (Bonferroni's method, $P < 0.01$).

Table1. Percentage (Number) of Neonates and Clinical Findings Based on Type of Conception

Clinical Characteristics	Type of Conception			*P* Value
	Spontaneous	Non-ART	ART	
Total, % (n)	80.2 (3,139)	9.9 (387)	9.9 (387)	
Singleton, % (n)	86.3 (2,710)	37.2 (144)	24.0(93)	< 0.001[1]
Twins, % (n)	13.7 (412)	59.2 (229)	72.9 (282)	< 0.001[1]
Triplets, % (n)	0.5 (17)	3.6 (14)	3.1 (12)	< 0.001[1]
Male gender, % (n)	55.1 (1,731)	51.4 (199)	51.9 (201)	0.22[1]
Gestational age, median (wk)	35.1	34.0	34.7	< 0.001[2]
Birth weight, mean (SD) (g)	2,273.5 (785.5)	1,891.4 (667.0)	2,021 (581.3)	< 0.001[2]
CS, % (n)	56.7 [a] (1,779)	82.9 [b] (321)	90.2 [c] (349)	< 0.001[1]
Maternal past illness[3], % (n)	18.8 [a] (591)	9.8 [b] (38)	9.8 [b] (38)	< 0.001[1]

ART : assisted reproductive technology ; CS : cesarean section.
[1] Chi-square test
[2] One-facture analysis of variance (ANOVA)
[3] Including hypertension, congenital heart disease, autoimmune disease, asthma, psychological disease, and diabetes mellitus
[a, b, c] Value with different letters are significantly different by Bonferroni's method (P<0.01)

To determine chronological changes in the number of admissions to the NICU in each group, we divided the study period into three portions (Table 2). Over 11 years, the percentage of non-ART births was almost constant; however, the percentage of ART births significantly increased from 2000 ($P < 0.001$). Since 2000, IFT accounted for 20% of NICU admissions. Next, we compared the rates of singleton and multiple births in each group between the three periods (Table 3). There was a significant difference in admission rates to the NICU for singleton births in the spontaneous group among the three periods ($P = 0.02$) ; however, a regular trend was not found. The percentage of singleton births in the ART group increased from 17.5% (1997-1999) to 33.2% (2004-2007) (Bonferroni's method, $P < 0.01$).

Table 2. Percentage (Number) of infants Conceived via Non-ART and ART in Three Time Periods

	Type of Conception	
	Non-ART	ART
1997-1999, % (n)	10.2 (89)	4.6 (40)
2000-2003, % (n)	8.9 (138)	12.5 (196)
2004-2007, % (n)	10.8 (160)	10.1 (151)
P value[1]	0.19	< 0.001

ART : assisted reproductive technology
[1] Chi-square test

Table 3. Percentage (Number) of Singleton and Multiple Gestations by Type of Conception over Three Time Periods

		1997-1999, % (n)	2000-2003, % (n)	2004-2007, % (n)	*P* value[1]
Spontaneous	Singleton	86.1 (637)	84.5 (1035)	88.4 (1,038)	0.02
	Multiple	13.9 (103)	15.5 (190)	11.6 (136)	NA
Non-ART	Singleton	32.6 (29)	40.6 (56)	36.9 (59)	0.47
	Multiple	67.4 (60)	59.4 (82)	63.1 (101)	NA
ART	Singleton	17.5 [a] (7)	18.4 [a, b] (36)	33.2 [b] (50)	0.004
	Multiple	82.5 (33)	81.6 (160)	66.9 (101)	NA

ART：assisted reproductive technology；NA：not analyzed
[1] Chi-square test
[a, b] Value with different letters are significantly different by Bonferroni's method (P<0.01)

Table 4 presents neonatal morbidity and mortality in each group. The rate of FGR in singleton births was significantly highest in the non-ART group (Bonferroni's method, $P < 0.01$). There were no significant differences in the percentages of LBW infants in any group among the three periods. In twin births, there was a significant difference in preterm delivery among the three groups ($P = 0.002$), with the lowest rate in the ART group.

Table 4. Morbidity and Mortality of Singleton and Twin Births in Each Group

		Spontaneous	Non-ART	ART	P value[1]
Singleton	n	2710	144	93	
	Preterm (%)	1,412 (52.1)	72 (50.0)	46 (49.5)	0.79
	LBW (%)	1,460 (53.9)	91 (63.2)	47 (50.5)	0.07
	FGR (%)	473 (17.5 [a])	52 (36.1 [b])	11 (11.8 [c])	< 0.001
	Anomaly (%)	570 (21.0)	28 (19.4)	10 (10.8)	0.05
	Death (%)	113 (4.2)	8 (5.6)	4 (4.3)	0.65
Twin	n	412	229	282	
	Preterm (%)	343 (83.3 [a])	183 (79.9 [a])	203 (72.0 [b])	0.002
	LBW (%)	376 (91.3)	220 (96.1)	261 (92.6)	0.08
	FGR (%)	109 (26.5)	67 (29.3)	95 (33.7)	0.12
	Anomaly (%)	38 (9.2)	16 (7.0)	30 (10.6)	0.36
	Death (%)	8 (1.9)	8 (3.5)	4 (1.4)	0.25

ART：assisted reproductive technology；LBW：low birth weight；FGR：fetal growth restriction
[1] Chi-square test
[a, b, c] Value with different letters are significantly different by Bonferroni's method (P<0.01)

Table 5 presents morbidity and mortality of twins in each group according to chorionicity. There was a significant difference among the three groups in the rates of LBW of DD twins ($P < 0.02$).

Table 5. Morbidity and Mortality of Twins in Each Group According to Chorionicity

		Spontaneous	Non-ART	ART	*P* value[1]
MD	n	228	15	12	
	Preterm, n (%)	198 (86.8)	12 (80)	12 (100)	0.29
	LBW, n (%)	214 (93.9)	15 (100)	12 (100)	0.42
	FGR, n (%)	60 (26.3)	5 (33.3)	2 (16.7)	0.62
	Anomaly, n (%)	22 (9.6)	1 (6.7)	1 (8.3)	0.92
	TTTS, n (%)	31 (13.5)	5 (29.4)	4 (36.4)	NA
	Discordant twin, n (%)	57/181 (31.5)	6/12 (50.0)	6/10 (60.0)	0.09
	Death, n (%)	7 (3.1)	0	0	0.65
DD	n	164	203	262	
	Preterm, n (%)	129 (78.7)	161 (79.3)	189 (72.1)	0.14
	LBW, n (%)	144 (87.8)	194 (95.6)	242 (92.4)	0.02
	FGR, n (%)	42 (25.6)	61 (30.0)	91 (34.7)	0.13
	Anomaly, n (%)	13 (7.9)	14 (6.9)	29 (11.1)	0.26
	Discordant twin n (%)	28/118 (23.7)	46/162 (28.4)	49/183 (26.8)	0.68
	Death, n (%)	1 (0.6)	8 (3.9)	4 (1.5)	0.06

MD：monochorionic diamniotic twin；DD：dichorionic diamniotic twin；LBW：low birth weight；FGR：fetal growth restriction；TTTS：twin to twin transfusion syndrome；NA：not analyzed
[1] Chi- square test

Discussion

This study revealed that infants conceived with IFT accounted for 20% of NICU admissions from 2000. The rate of twins born following IFT procedures was high. The rate of singleton births increased over time in the ART group. The CS rates were high in both the ART and non-ART groups. There were no significant differences in congenital anomalies or neonatal deaths among the three groups.

IFT births account for 2% of live births in Japan[1]. If this percentage is of the same order in Tochigi Prefecture, this suggests that neonates born via IFT have a 10 times higher risk of admission to the NICU than neonates born without IFT. Therefore, this indicates that a NICU is necessary if IFT is conducted in the catchment area.

Multiple gestations are one of the major complications of IFT. Recently, the percentage of multiple gestations from IFT was reported to decrease to around 13.0% in Japan[1, 3]. We reported that the percentage of singletons conceived with ART increased significantly from 17.5% (1997-1999) to 33.2% (2004-2007). The decrease in multiple births is likely the result of single embryo transfers (SETs) in ART.

CS rates in the ART and non-ART groups were higher than in the spontaneous group. A high CS rate could be related to the high rates of multiple gestations in IFT groups. Moreover, the CS rates were high even in singleton pregnancies in IFT groups. We did not investigate why CS had been chosen in each case. However, the indications for CS may be related to not only medical but also social relevancies. However, CS is associated with many neonatal complications, including

respiratory distress, and hypoglycemia[12, 13]. This association may help explain why births after IFT frequently lead to neonatal admissions to the NICU.

This study also reported that the maternal past illnesses were higher in the spontaneous group than in IFT groups. This could be related to the fact that our center is the only tertiary center in Tochigi Prefecture. Thus, it is likely that mothers who have past illness are directed to our hospital.

The latest reviews suggest that there is a significant increase of FGR after ART[5]. In this study, a significant increase in FGR for non-ART singletons was found; however, it was not found in the ART group. We cannot determine why the difference in results occurred.

One of the greatest concerns of IFT is congenital anomalies. In this study, there were no significant differences in the incidence of anomalies between different types of conception. This result is consistent with several previous reports[5, 3, 7, 14, 15]. The relatively high rate of anomalies in spontaneous singletons in this study was probably also due to the characterization of our hospital as a tertiary care center. Many patients with congenital anomalies were admitted to our NICU from other centers to undergo surgery. Conversely, recent reviews suggest that the rate of congenital anomalies is higher in infants born with IFT than infants born without IFT[5, 7, 8].

In conclusion, over the past 10 years, no studies have described the impact of IFT on NICU in a temporal manner. In this study, we found a substantial amount of cases of FGR in singletons conceived with IFT, as well as CS, in pregnancies following IFT. Infants from IFT are increasing, and perinatal intensive care is indispensable for them.

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不妊治療後に出生した児の11年間にわたる経年的変化とその臨床像

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要　約

不妊治療（Infertility treatment, IFT）の技術が進歩して，IFT により出生した児は増えている。IFT は産科医療にも，小児科とくに新生児医療にも影響を与えている。たとえば，双胎，低体重児，早産児，FGR は増加しており，ほかに奇形も増加していると推測されている。これらは自ずと児の罹患率をあげ，新生児医療を圧迫するが，実際に単一の新生児集中治療部（neonatal intensive care unit, NICU）に具体的にどのような影響を及ぼしているのか，という報告はない。そこで自治医大 NICU に11年間の長期間にわたり入院した3913人を対象として，妊娠方法別に，その特徴，および合併症について，患者推移を明らかにし，これらの変化が新生児医療にどのように影響を及ぼしたか述べた。
（キーワード：不妊治療，生殖補助医療，NICU，双胎，低出生体重児）

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