

Outcomes of Very Preterm Neonates Born by Assisted Reproductive Techniques (ART): A Propensity Score Matched Retrospective Cohort Study

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Objective: To compare outcomes of preterm neonates born through assisted reproduction techniques (ART) and non-ART conception. **Methods:** This retrospective cohort study included very preterm neonates (26 weeks to 31 weeks) admitted to our neonatal unit over a six year period from 2014 to 2019. The primary outcome was composite adverse outcome of mortality or any of the major morbidities i.e., intraventricular hemorrhage (IVH) grade ≤ 3 , periventricular leukomalacia (PVL) grade ≤ 2 , bronchopulmonary dysplasia (BPD) at 36 weeks, and retinopathy of prematurity (ROP) requiring treatment. **Results:** Total of 759 neonates (253 in ART group, 506 in non-ART group) were included after propensity score matching for gestational age, sex, and small for gestational age (SGA). Neonates in ART group had similar rates of composite adverse outcome [aOR (95% CI) 0.86 (0.55 – 1.36)], mortality [0.93, (0.53-1.64)] BPD [1.18, (0.37 – 3.76)]; ROP requiring treatment [0.49 (0.14-1.71), and other morbidities. **Conclusion:** Very preterm neonates born through ART were not at increased risk of adverse neonatal outcomes.

Key words: Chromosomal microarray analysis, Etiology, Exome sequencing.

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In pregnancies resulting from assisted reproductive techniques (ART), the risk of spontaneous preterm birth, low birthweight [1], obstetric and perinatal complications were higher [2]. World Health Organization (WHO) definition of ART includes all treatments or procedures of invitro handling of both human oocytes and sperm, or of embryos for the purpose of establishing a pregnancy [3]. This definition by WHO does not include artificial insemination. Along with the maternal age, invitro manipulation, epigenetic disorders including abnormal methylation, cryopreservation of gamete or embryo, and invitro culture environment may influence the outcomes of ART [4], which may potentially contribute to adverse outcomes. It is important to understand this pathophysiologic plausibility for the inclusion of neonates into ART group while investigating their outcomes. Studies on the outcomes of very preterm neonates born through ART are limited and have conflicting results with no data from low- and middle-income countries [5-14]. Most of the previous studies didn't adhere to WHO definition and included major congenital anomalies, which might independently affect the results. In this study, we planned to evaluate the outcomes of very preterm neonates born by ART, defined as per the WHO definition.

METHODS

This retrospective cohort study was conducted in level III NICU of a tertiary care neonatal unit in South India after the approval by the Institute's ethics committee. Data of all consecutively born very preterm neonates (26 weeks, 0 days to 31 weeks, 6 days) over a 6-year period (January, 2014 to December, 2019) was retrieved from the electronic medical records of the unit. Neonates with major congenital anomalies, those transferred early to other centers, and those who did not receive active treatment were excluded. Neonates born before 26 weeks and below 600 g birthweight were excluded, as they were not routinely treated in our unit.

As per the WHO definition, infants born through invitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) methods were included in the ART group [4]. Neonates born through ovulation induction (OI) and intrauterine insemination (IUI) were included in non-ART group. Gestational age was estimated based on the fertilization date (oocyte retrieval+14 days) and first trimester ultrasound, and was confirmed by new Ballard score postnatally. Small for gestational age (SGA) and severe SGA were defined as birthweight less than 10th centile and

3rd centile for gestational age, respectively as per Fenton 2013 growth charts. Bronchopulmonary dysplasia (BPD) was defined as requirement of any respiratory support at 36 weeks post-menstrual age (PMA). Intra-ventricular hemorrhage (IVH), periventricular leukomalacia (PVL) and retinopathy of prematurity (ROP) treatment were followed as per Volpe classification, DeVries classification and ETROP recommendations, respectively. Extrauterine growth restriction (EUGR) was defined as discharge weight <10th centile for discharge PMA and sex on Fenton growth charts. The primary outcome was to compare the composite adverse outcome (defined as in-hospital mortality or one of the major morbidities i.e., IVH grade 3 or more, PVL grade 2 or more, BPD, and ROP requiring treatment) between very preterm neonates born through ART and non-ART conception.

Statistical analysis: The incidence of adverse composite outcome in the very preterm group from the previous hospital data of 5 years was 20% [15]. Assuming that the exposed group (ART) might have 10% higher incidence in the adverse composite outcome, with the ratio of exposed to unexposed group of 1:2, 80% power and 5% two-sided alpha error, the required minimum sample size was 231 subjects in the exposed group and 461 subjects in unexposed group. Propensity matching was done by matching for gestational age, sex and SGA by using nearest neighbour matching (NNM) method without replacement, at a 1:2 ratio. Univariable and multivariable binary logistic regression and linear regression adjusting for maternal age, gestational diabetes and gestation type (multifetal pregnancy) was performed to assess the association of ART and non-ART groups with various binary and numeric outcomes, respectively. IBM SPSS version 22.0 was used for statistical analyses.

RESULTS

Among the total of 1371 neonates born during the study period, twenty five (1.8%) neonates had major congenital anomalies and 279 (20.3%) neonates were either transferred to another hospital or did not undergo complete treatment at study hospital or had incomplete data, leaving 1067 neonates for analysis. The distribution of excluded neonates was similar in ART (64/317, 20%) and non-ART groups (230/1,057, 22%). The mean (SD) gestational age and mean birthweight of excluded infants were 28.6 (1.6) weeks and 1034 (250) g, respectively. The reasons for transfer to other hospitals before completion of treatment were financial (availability of insurance at other hospitals in 69.7%) and unsure outcomes due to extreme prematurity (30.3%).

After the propensity score matching, a total of 759 neonates (253 in ART group and 506 in non-ART group)

were included in the final analysis. The mean (SD) gestational age of the study population was 29.1 (1.5) weeks and mean (SD) birthweight was 1172 (285) g. The overall incidence of in-hospital mortality and the composite adverse outcome were 11.7% ($n=89$) and 22.9% ($n=174$), respectively. After propensity score matching, the groups were comparable in neonatal baseline characteristics but the maternal characteristics of maternal age, primiparity, multifetal gestation and gestational diabetes, were higher in the ART group (**Table I**).

Neonates in ART group had similar rates of composite adverse outcome, mortality, morbidities and discharge characteristics compared to neonates conceived by non-ART conception (**Tables II**). After multivariable logistic regression analysis adjusted for maternal age, type of gestation (multifetal pregnancy) and gestational diabetes, the major outcomes remained similar (**Table II**). On multivariate analysis, only the incidence of hemodynamically significant patent ductus arteriosus (HsPDA) requiring treatment was higher in non-ART group neonates (**Table III**).

Table I Characteristics of Neonates Born By ART and Non-ART

Characteristic	ART ($n=253$)	Non-ART ($n=506$)	P value
Maternal age (y) ^a	32.73 (4.43)	28.86 (4.15)	<0.001
Primigravida	155 (61.3)	242 (47.8)	<0.001
Primipara	232 (91.7)	328 (64.8)	<0.001
Multifetal gestational	186 (73.5)	128 (25.3)	<0.001
PIH	112 (44.3)	203 (40.1)	0.27
Gestational diabetes	51 (20.2)	62 (12.3)	0.004
Gestational age (wk) ^a	29.1 (1.66)	29.2 (1.53)	0.27
Birthweight (g) ^a	1175.81 (310.3)	1170.85 (271.8)	0.82
Male sex	131 (51.8)	249 (49.2)	0.5
SGA	35 (13.8)	64 (12.7)	0.65
Severe SGA	2 (0.8)	7 (1.4)	0.73
Doppler abnormalities	38 (15)	105 (20.8)	0.06
No antenatal steroids	10 (4)	21 (4.2)	0.9
Chorioamnionitis	21 (8.3)	42 (8.3)	1.0
PPROM	84 (33.2)	157 (31)	0.54
Cesarean delivery	216 (85.4)	413 (81.6)	0.2
APGAR <7 at 5 min	28 (11.1%)	55 (10.9)	0.93
Resuscitation at birth	66 (26.1%)	138 (27.3)	0.73

All values in no. (%) or ^amean (SD). ART: artificial reproductive techniques; PIH: pregnancy induced hypertension; SGA: small for gestational age; PPRM: preterm premature rupture of membranes.

Table II Mortality and Major Morbidities in Infants Born Through ART and Non-ART

Outcome	ART (n=253)	Non-ART (n =506)	aOR (95% CI)	P value
BPD (respiratory support at 36 wk PMA)	8 (3.2)	12 (2.4)	1.18 (0.37-3.76)	0.78
IVH grade ≥ 3	16 (6.3)	22 (4.3)	1.5 (0.62-3.6)	0.36
PVL grade ≥ 2	8 (3.2)	11 (2.2)	1.7 (0.52-5.57)	0.38
ROP requiring treatment	4 (1.6)	18 (3.6)	0.49 (0.14-1.71)	0.26
Mortality	35 (13.8)	54 (10.7)	0.93 (0.53-1.64)	0.8
Composite adverse outcome (any of the above 5)	56 (22.1)	118 (23.3)	0.86 (0.55-1.36)	0.53

All values in no. (%). aOR=adjusted odds ratio, adjusted for maternal age, gestation type, gestation diabetes. ART: artificial reproductive techniques; BPD: bronchopulmonary dysplasia; IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia; ROP: retinopathy of prematurity.

DISCUSSION

In our study, very preterm neonates born through ART conception had no increase in mortality, major morbidities and composite adverse outcome as compared to those born through non-ART conception, after propensity score matching. The higher incidence of HsPDA requiring treatment on multivariate analysis in neonates born through non-ART did not result in increased duration of respiratory support and need for surgical ligation.

A large study by Heo, et al. [11] from Korean Neo-natal Network (KNN) registry investigated the outcomes of very low birth weight (VLBW) neonates born after IVF conception concluded that VLBW neonates born through IVF conception had comparable or better outcomes. These differences were attributed to likely better access to high

quality health care for women who underwent IVF conception as they belonged to high socioeconomic status and probable differences in chorionicity. The study included neonates with congenital anomalies and did not adjust the analysis for the variability of participating centers. Picaud, et al. [12] from France reported higher survival without severe morbidity and less BPD in very preterm neonates born through ART which were described by the differences in pregnancy care (close monitoring antenatally) and neonatal characteristics (more inborn, better mature and more birthweight in ART group). This study included the neonates born through OI conception (where oocyte handling is not done) into ART group.

In a very large multicentric propensity matched study on neonates less than 34 weeks by Ahmed, et al. [13], BPD

Table III Outcomes in Infants Born Through ART and Non-ART

Outcome	ART (n=253)	Non-ART (n =506)	aOR (95% CI)	P value
RDS	171 (67.6)	349 (69)	0.72 (0.48-1.07)	0.14
Surfactant	161 (63.6)	330 (65)	1.41 (0.95-2.1)	0.09
Duration of respiratory support (total) ^b	6 (2-15)	7 (3-14)	0.99 (0.99-1.01)	0.92
Duration of respiratory support (invasive) ^b	0 (0-2)	0 (0-2)	0.98 (0.94-1.03)	0.46
More than 28 d of oxygen requirement	43 (17)	79 (15.6)	0.88 (0.51-1.51)	0.65
Hs-PDA requiring treatment	66 (26.1)	132 (26.1)	0.64 (0.41-0.99)	0.046
PDA-surgical ligation	5 (2)	4 (0.8)	2.5 (0.45-13.9)	0.3
NEC stage 2A or more	17 (6.7)	43 (8.5)	0.57 (0.27-1.2)	0.14
Culture positive sepsis	62 (24.5)	138 (27.3)	0.65 (0.42-1.02)	0.06
Any Grade IVH	58 (22.9)	146 (28.9)	0.81 (0.52-1.25)	0.33
Any ROP	22 (8.7%)	61 (12.1)	0.63 (0.33-1.21)	0.16
Discharge PMA (wk) ^b	34 (32-35)	34 (32-35)	1.02 (0.97-1.08)	0.52
Discharge weight (g) ^b	1520 (1420-1660)	1480 (1420-1620)	1 (1-1.001)	0.39
EUGR	217 (70)	328 (72.7)	0.93 (0.65-1.37)	0.69

All values are in no. (%) or ^bmedian (IQR). aOR=adjusted odds ratio, adjusted for maternal age, gestation type, gestational diabetes; ART: artificial reproductive techniques; RDS: respiratory distress syndrome; HsPDA: hemodynamically significant patent ductus arteriosus; NEC: necrotizing enterocolitis; IVH: intraventricular hemorrhage; ROP: retinopathy of prematurity; PMA: post menstrual age; EUGR: extrauterine growth restriction.

WHAT THIS STUDY ADDS?

- Very preterm neonates born through assisted reproduction techniques (ART) are not at increased risk of short term adverse neonatal outcomes.

and exposure to chronic respiratory medications were higher in neonates born through IVF conception, which was possibly postulated to epigenetic differences. The inclusion of neonates born by ICSI and IUI conception was not mentioned. Compared to this study, oxygen requirement for >28 days, duration of respiratory support and BPD were similar in both the groups in our study. A metaanalysis by Gao, et al. [14] on the effect of ART on ROP showed that the use of IVF was associated with higher risk of ROP occurrence. Our study, with a relatively smaller sample size, did not show any increase in incidence of ROP and severe ROP.

Other studies have shown no differences in outcomes of preterm neonates born through ART but these had differences in the inclusion criteria used [5-9], with some studies including neonates born by IUI and OI conception in ART group [8], and other studies excluding OI conception from the analysis [5,6,9]; whereas, one of those included neonates with congenital anomalies [5]. Including congenital anomalies might affect the reliability of outcomes as these can increase the adverse outcomes of preterm neonates due to their increased need for interventions.

The key strengths of the study were using WHO-ART definition, minimizing the potential confounding by key parameters using propensity score matching, and restriction of the study to infants without major anomalies. Residual confounding was also addressed by presenting adjusted estimates during analysis. Major limitation was exclusion of nearly 20% of eligible infants but this exclusion was not different between the two study groups, so the amount selection bias it could have introduced was expected to be minimal. Being a single center data may be a limitation but conversely, single center data may also decrease the variability of the practices. Also, we need more long-term follow-up studies on this important issue.

Very preterm neonates born after ART did not have increased risk of short-term neonatal outcomes compared to neonates born without ART.

REFERENCES

1. Cavoretto P, Candiani M, Giorgione V, et al. Risk of spontaneous preterm birth in singleton pregnancies conceived after IVF/ICSI treatment: Meta analysis of cohort studies. *Ultrasound Obstet Gynecol.* 2018;51:43-53.
2. Pandey S, Shetty A, Hamilton M, et al. Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: A systematic review and meta-analysis. *Hum Reprod Update.* 2012;18:485-503.
3. Zegers-Hochschild F, Adamson GD, de Mouzon J, et al. The international committee for monitoring assisted reproductive technology (ICMART) and the world health organization (WHO) revised glossary on ART terminology, 2009. *Hum Reprod.* 2009;24:2683-7.
4. Tarin JJ, García Pérez MA, Cano A. Assisted reproductive technology results: Why are live birth percentages so low? *Mol Reprod Dev.* 2014;81:568-83.
5. Al-Hathlol K. Relationship between in vitro fertilization and neonatal outcomes in very low birth weight preterm infants. *Am J Perinatol.* 2018;35:1113-8.
6. Schimmel MS, Hammerman C, Lusky A, Reichman B. Very low-birth-weight-infants conceived by in vitro fertilization are not at higher risk for mortality and morbidity: a population-based study. *Fertil Steril.* 2006;85:907-12.
7. Chiarelli L, Mirea L, Yang J, Lee SK, Shah PS, Canadian Neonatal Network. Neonatal outcomes in very preterm singleton infants conceived using assisted reproductive technologies. *Am J Perinatol.* 2015;32:515-22.
8. Corchia C, Da Frè M, Di Lallo D, et al. Mortality and major morbidities in very preterm infants born from assisted conception or naturally conceived: results of the area-based ACTION study. *BMC Pregnancy Childbirth.* 2014;14:307.
9. Turker G, Doger E, Arýsoy AE, et al. The effect of IVF pregnancies on mortality and morbidity in tertiary unit. *Ital J Pediatr.* 2013;39:17.
10. Messerschmidt A, Olischar M, Birnbacher R, et al. Perinatal outcome of preterm infants <1500g after IVF pregnancies compared with natural conception. *Arch Dis Child Fetal Neonatal Ed.* 2010;95:F225-9.
11. Heo JS, Lee HJ, Lee MH, Choi CW. Comparison of neonatal outcomes of very low birth weight infants by mode of conception: in vitro fertilization versus natural pregnancy. *Fertil Steril.* 2019;111:962-70.
12. Picaud JC, Chaliès S, Combes C, et al. Neonatal mortality and morbidity in preterm infants born from assisted reproductive technologies. *Acta Paediatr.* 2012;101:846-51.
13. Ahmad KA, Bennett MM, Rayburn P, et al. Outcomes of preterm infants conceived with in vitro fertilization. *J Perinatol.* 2019;39:717-22.
14. Gao L, Shao W, Li N, et al. The risk of retinopathy of prematurity in the infants following assisted reproductive technology: A meta-analysis. *Biomed Res Int.* 2019; 2095730.
15. Anne RP, Vardhelli V, Oleti TP, et al. Propensity-matched comparison of very preterm small-and appropriate-for-gestational-age neonates. *Indian J Pediatr.* 2022;89:59-66.