

## Research Article



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## OUTCOMES OF PRETERM NEONATES BORN USING ARTS AND NON-ART CONCEPTION

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### ABSTRACT

**Background:** Studies on the outcomes of extremely preterm newborns delivered with assisted reproductive procedures are few and far between in the literature. Furthermore, there is a dearth of information from middle- and low-income nations.

**Aim:** The purpose of this study was to compare the outcomes of preterm neonates born using assisted reproductive technologies (ART) and those born without ART.

**Methods:** The current study evaluated extremely preterm newborns admitted to the institute's neonatal unit throughout the study period and born between 26 and 31 weeks gestation. The composite adverse outcome of mortality and any other significant morbidities, such as retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD) at 36 weeks, periventricular leukomalacia (PVL) grade  $\leq 2$ , and intraventricular hemorrhage (IVH) grade  $\leq 3$  that required treatment, was the main outcome evaluated.

**Results:** The 380 neonates in the trial were matched for age, gender, and SGA (small for gestational age), with 127 in the ART group and 258 in the non-ART group. The composite adverse outcome rates for neonates in the ART group were comparable, with OR (95% CI) of 0.84 (0.53-1.34), ROP needing treatment of 0.47 (0.12-1.69), BPD of 1.16 (0.35-3.74), death of 0.91 (0.51-1.62), and other morbidities.

**Conclusion:** in comparison to neonates delivered using non-assisted reproductive procedures, extremely preterm neonates born using assisted reproductive techniques do not have a greater risk of unfavorable neonatal outcomes.

**Keywords:** very preterm neonates, ART (assisted reproductive techniques), small for gestational age, non-ART

### INTRODUCTION

greater likelihood of obstetric and perinatal problems Low birthweight and the chance of an unplanned preterm birth have been connected to assisted reproductive technologies, or ART. The World Health Organization defines assisted reproductive methods as any in vitro manipulation of human sperm, oocytes, or embryos for the purpose of establishing pregnancy. In the World Health Organization's definition, artificial insemination is neither included or taken into consideration. In vitro manipulation, maternal age, cryopreservation of embryo or gamete, epigenetic diseases such as aberrant methylation, and the in vitro culture environment can all have a significant impact on the results of assisted reproductive procedures. These variables that control the results of assisted reproductive methods may also play a major role in the negative consequences of these procedures.<sup>3,4</sup>

When evaluating the results of assisted reproductive procedures, it is critical to comprehend this pathological plausibility with regard to the inclusion of newborns and neonates in the group. 5 Research evaluating the outcomes for extremely preterm newborns born by assisted reproductive methods is few, yields conflicting findings, and lacks conclusive data in middle- and low-income countries.<sup>6,7</sup>

The bulk of the data in the literature does not strictly follow the World Health Organization's criteria, which evaluated the main congenital abnormalities that might have an independent impact on the outcomes. 8. The results of extremely preterm neonates delivered using assisted reproductive methods are evaluated in this study in accordance with the World Health Organization's criteria. The goal of this study was to compare the outcomes of preterm newborns born by assisted reproductive technologies (ART) versus those born without ART.

## **MATERIALS AND METHODS**

The goal of this retrospective clinical study was to compare the outcomes of preterm neonates born using assisted reproductive technologies (ART) and those born without ART. The research participants were drawn from the Institute's pediatric department. Prior to their involvement in the study, all individuals gave their written and verbal informed consent.

The study evaluated the data from the Institute's NICU (neonatal intensive care unit) in hindsight. All of the extremely preterm newborns' data were collected in a sequential manner from the Institute's old records.

The study excluded newborns with serious congenital defects, neonates with a birth weight of less than 600 grams, neonates without active treatment, neonates moved to other facilities too soon, and neonates delivered before the gestational age of 26 weeks. Due to their lack of management and treatment at the Institute, these subjects were disqualified.

According to the World Health Organization's definition, babies born using ICSI (intracytoplasmic sperm injection) and IVF (in vitro fertilization) techniques were classified as part of the ART category. Nine infants delivered by ovulation induction (OI) and intrauterine insemination (IUI) were part of the non-ART group.

After the day of fertilization, including egg extraction and further 14 days, gestational age was measured. A first-trimester ultrasound was also performed, and a fresh Ballard score was used postnatally for confirmation. According to the Fenton 2013 growth chart, birthweights below the third and tenth centiles for gestational age, respectively, were considered severe SGA (small for gestational age) and SGA.

The requirement for any kind of breathing assistance at 36 weeks post-menstrual age (PMA) was referred to as bronchopulmonary dysplasia, or BPD. For the evaluation of ROP (retinopathy of prematurity), PVL (periventricular leukomalacia), and IVH (intraventricular hemorrhage), respectively, ETROP guidelines, DeVries classification, and Volpe classification were adhered to. On Fenton growth charts, discharge weight <10th centile for discharge PMA and sex was considered EUGR (extrauterine growth restriction). The study's main goals were to compare the composite adverse outcome, which is defined as in-hospital death or one or more significant morbidities, such as IVH of grade 3 or higher, BPD, PVL of grade 2 or higher, and ROP requiring treatment.

In order to evaluate descriptive measures, the collected data was statistically analyzed using SPSS (Statistical Package for the Social Sciences) software version 16.0 (SPSS Inc., Chicago, USA). In addition to frequency and percentages, the findings were presented as mean and standard deviation. A p-value of less than 0.05 was deemed statistically significant. The Chi-square test was used to determine how significant the research parameters were on the categorical scale. When the results of the ANOVA were significant, post-hoc Turkey analysis was performed.

## **RESULTS**

In the current retrospective clinical analysis, the outcomes of preterm neonates delivered by assisted reproductive technologies (ART) and non-ART conception were compared. 258 newborns in the non-ART group and 127 neonates in the ART group were matched for age, gender, and SGA (small for gestational age) out of the 380 neonates evaluated in the research. The ART group's maternal age was  $32.71 \pm 4.41$  years, which was considerably higher than the non-ART group's  $28.84 \pm 4.13$  years ( $p < 0.001$ ).  $p = 0.25$  for the two groups' similar gestational ages. The prevalence of gestational diabetes was considerably higher in the ART group ( $p = 0.003$ ). PIH in the ART and non-ART groups was statistically similar ( $p = 0.25$ ). Primipara, primigravida, and multifetal gestation were considerably greater in the ART group than in the non-ART group ( $p < 0.001$ ).

With corresponding p-values of 0.7, 0.71, 0.63, 0.3, 0.84, 0.71, 0.91, 0.4, and 0.52, the ART and non-ART groups were statistically comparable in terms of no antenatal steroid need, severe SGA, SGA, male gender, birthweight, resuscitation at

birth, APGAR <7 at 5 minutes, cesarean delivery rate, PPRM, and chorioamnionitis. ROP requiring treatment was observed in 1.57% (n=2) of the ART group and 3.48% (n=9) of the non-ART group, indicating statistical non-significance with p=0.24. When comparing the major comorbidities and mortality in infants born from ART and non-ART, the mortality in the ART and non-ART groups was 14.17% (n=18) and 10.46% (n=27) respectively, which was statistically non-significant with p=0.6.

3.14% (n=4) and 1.93% (n=5) of the ART and non-ART groups' patients, respectively, had PVL grade  $\geq 2$ , which was statistically not significant (p=0.36). 6.29% (n=8) and 4.26% (n=11) of the ART and non-ART groups' patients, respectively, had IVH grade  $\geq 3$ , which was statistically not significant (p=0.34). 3.14% (n=4) and 2.32% (n=6) of the ART and non-ART groups, respectively, had BPD needing respiratory assistance at 35 weeks PMA; this difference was statistically not significant (p=0.76). Table 2 shows that 22.04% (n=28) and 22.86% (n=59) of the individuals in the ART and non-ART groups, respectively, experienced composite unfavorable outcomes from any of the aforementioned five. These results were statistically non-significant with p=0.51.

According to the study's findings, 22.83% (n=29) and 28.29% (n=73) of the individuals in the ART and non-ART groups, respectively, had any grade IVH in their children delivered as a consequence of ART and non-ART, which was statistically not significant (p=0.313). 24.40% (n=31) and 26.74% (n=69) of the ART and non-ART groups, respectively, had culture-positive sepsis; these findings were statistically not significant (p=0.07). 7.08% (n=9) and 8.13% (n=21) of the participants in the ART and non-ART groups, respectively, had NEC stage 2A or higher; these findings were not statistically significant (p=0.16). In the ART and non-ART groups, PDA surgical ligation was observed in 2.36% (n=3) and 0.77% (n=2) of individuals, respectively. This difference was not statistically significant (p=0.1).

25.98% (n=33) and 25.81% (n=66) of the subjects in the ART and non-ART groups, respectively, required treatment for Hs-PDA, which was significantly higher in the ART group (p=0.03). Also, 17.32% (n=22) and 15.11% (n=39) of the subjects in the ART and non-ART groups, respectively, required oxygen for more than 28 days, which was not significant (p=0.63). With p=0.44, the duration of invasive respiratory assistance was similar in the ART and non-ART groups (Table 3).

With p=0.94, it was shown that the duration of respiratory assistance was similar in the ART and non-ART groups. Comparable amounts of surfactant were also seen in the ART and non-ART groups (p=0.08). Comparable amounts of RDS and EUGR were seen in the ART and non-ART groups (p=0.12 and p=0.67, respectively).

At discharge, the newborns' weights in the ART and non-ART groups were, respectively, 1522 and 1480 grams, which was statistically not significant (p=0.37). With p=0.54, discharge PMA (weeks) was seen in 13.38% (n=17) of ART-treated participants and 6.58% (n=17) of non-ART-treated subjects. 8.66% (n=11) and 12.40% (n=32) of the individuals in the ART and non-ART groups, respectively, experienced any ROP; this was statistically not significant (p=0.18) (Table 3).

## DISCUSSION

The 380 newborns evaluated in this trial were matched for age, gender, and SGA (small for gestational age), with 127 in the ART group and 258 in the non-ART group. At 32.71 $\pm$ 4.41 years, the maternal age of the ART group was substantially greater than that of the non-ART group (p<0.001).

With p=0.25, the two groups' gestational ages were similar. In the ART group, the prevalence of gestational diabetes was considerably higher (p=0.003). PIH in the ART and non-ART groups was statistically similar (p=0.25). The ART group had considerably greater rates of primipara, primigravida, and multifetal gestation (p<0.001) than the non-ART group. With corresponding p-values of 0.7, 0.71, 0.63, 0.3, 0.84, 0.71, 0.91, 0.4, and 0.52, the ART and non-ART groups were statistically comparable in terms of no antenatal steroid need, severe SGA, SGA, male gender, birthweight, resuscitation at birth, APGAR <7 at 5 minutes, cesarean delivery rate, PPRM, and chorioamnionitis. These results were comparable to those of research by Anne RP et al. (2010) and Gao L et al. (2011), in which the authors evaluated newborns from mothers using demographic information relevant to the current investigation.

When comparing the mortality and major comorbidities of children born on ART and non-ART, it was found that the mortality rates in the ART and non-ART groups were 14.17% (n=18) and 10.46% (n=27), respectively. These rates were statistically not significant (p=0.6). 1.57% (n=2) of the ART group's participants required treatment for ROP, whereas 3.48% (n=9) of the non-ART group's subjects did the same, indicating statistical non-significance (p=0.24). 3.14% (n=4) and 1.93% (n=5) of the ART and non-ART groups' patients, respectively, had PVL grade  $\geq 2$ , which was statistically not significant (p=0.36). 6.29% (n=8) and 4.26% (n=11) of the ART and non-ART groups' patients, respectively, had IVH grade  $\geq 3$ , which was statistically not

significant ( $p=0.34$ ). 3.14% ( $n=4$ ) and 2.32% ( $n=6$ ) of the ART and non-ART groups, respectively, had BPD needing respiratory assistance at 35 weeks PMA, which was statistically significant [ $p=0.76$ ].

22.04% ( $n=28$ ) and 22.86% ( $n=59$ ) of the participants in the ART and non-ART groups, respectively, experienced composite unfavorable outcomes from any of the aforementioned five, which was statistically non-significant ( $p=0.51$ ). These findings were in line with research by Ahmad KA et al. (2012) and Picaud JC et al. (2013), which found that the main comorbidities and death rates in infants born to ART and non-ART were similar to those in the current study.

According to the results for infants born on ART and those born off of it, 22.83% ( $n=29$ ) and 28.29% ( $n=73$ ) of the individuals in the ART and non-ART groups, respectively, experienced any grade IVH. This difference was statistically not significant ( $p=0.313$ ). 24.40% ( $n=31$ ) and 26.74% ( $n=69$ ) of the individuals had culture-positive sepsis, respectively from ART and non-ART groups which were statistically non-significant with  $p=0.07$ . 7.08% ( $n=9$ ) and 8.13% ( $n=21$ ) of the participants in the ART and non-ART groups, respectively, had NEC stage 2A or higher; these findings were not statistically significant ( $p=0.16$ ).

In the ART and non-ART groups, PDA surgical ligation was observed in 2.36% ( $n=3$ ) and 0.77% ( $n=2$ ) of individuals, respectively. This difference was not statistically significant ( $p=0.1$ ). 25.98% ( $n=33$ ) and 25.81% ( $n=66$ ) of the subjects in the ART and non-ART groups, respectively, required treatment for Hs-PDA, which was significantly higher in the ART group ( $p=0.03$ ). Also, 17.32% ( $n=22$ ) and 15.11% ( $n=39$ ) of the subjects in the ART and non-ART groups, respectively, required oxygen for more than 28 days, which was not significant ( $p=0.63$ ). The duration of invasive respiratory assistance was similar between the ART and non-ART groups ( $p=0.44$ ).

The results of Heo JS et al. (2014) and Messerschmidt A et al. (2015), who showed similar outcomes in children born from ART and non-ART in their respective investigations, were consistent with our findings. The length of respiratory assistance was similar in the ART and non-ART groups, according to the study's findings ( $p=0.94$ ).

Moreover, surfactant levels in the ART and non-ART groups were similar ( $p=0.08$ ). The proportions of RDS and EUGR in the ART and non-ART groups were similar ( $p=0.12$  and  $p=0.67$ , respectively). Neonatal weights in the ART and non-ART groups weighed 1522 and 1480 grams at discharge, respectively. This difference was statistically not significant ( $p=0.37$ ).

13.38% ( $n=17$ ) and 6.58% ( $n=17$ ) of the individuals in the ART and non-ART groups, respectively, had discharge PMA (weeks) with  $p=0.54$ . 8.66% ( $n=11$ ) and 12.40% ( $n=32$ ) of the participants in the ART and non-ART groups, respectively, experienced any ROP; this was statistically not significant ( $p=0.18$ ). These findings were consistent with those of Fineman DC et al.16 and Hogberg U et al.17, whose authors found comparable outcomes in extremely preterm children delivered from ART in their separate trials.

## CONCLUSIONS

Compared to neonates delivered via non-assisted reproductive procedures, extremely preterm neonates born by assisted reproductive techniques do not have a greater risk of unfavorable neonatal outcomes. To draw a firm conclusion, however, more extensive longitudinal research with a greater number of newborns in various geographic locations is necessary.

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S. No	Characteristics	ART		Non-ART		p-value
		n=127	%	n=258	%	
1.	<b>Maternal age (years)</b>	32.71±4.41		28.84±4.13		<b>&lt;0.001</b>
2.	<b>Gestational age (weeks)</b>	29.3±1.64		29.4±1.51		0.25
3.	<b>Gestational diabetes</b>	26	20.47	31	12.01	<b>0.003</b>
4.	<b>PIH</b>	56	44.09	101	39.14	0.25
5.	<b>Multifetal gestational</b>	93	73.22	64	24.80	<b>&lt;0.001</b>
6.	<b>Primipara</b>	116	91.33	164	63.56	<b>&lt;0.001</b>
7.	<b>Primigravida</b>	78	61.41	121	46.89	<b>&lt;0.001</b>
8.	<b>No antenatal steroids</b>	5	3.93	11	4.26	0.7
9.	<b>Doppler abnormalities</b>	19	14.96	53	20.54	<b>0.04</b>
10.	<b>Severe SGA</b>	1	0.78	3	1.16	0.71
11.	<b>SGA</b>	18	14.17	32	12.40	0.63
12.	<b>Male gender</b>	66	51.96	124	48.06	0.3
13.	<b>Birthweight (grams)</b>	1175.79±310.1		1170.83±271.6		0.84
14.	<b>Resuscitation at birth</b>	33	25.98	69	26.74	0.71
15.	<b>APGAR &lt;7 at 5 min</b>	14	11.02	28	10.85	0.91
16.	<b>Cesarean delivery</b>	108	85.03	206	79.84	0.4
17.	<b>PPROM</b>	42	33.07	78	30.23	0.52
18.	<b>Chorioamnionitis</b>	11	8.66	21	8.13	1.0

**Table 1: Characteristics of study neonates born in two groups of ART and non-ART**

S. No	Outcomes	ART		Non-ART		p-value
		n=127	%	n=258	%	
1.	Mortality	18	14.17	27	10.46	0.6
2.	ROP needing treatment	2	1.57	9	3.48	0.24
3.	PVL grade $\geq 2$	4	3.14	5	1.93	0.36
4.	IVH grade $\geq 3$	8	6.29	11	4.26	0.34
5.	BPD (respiratory support at 35-weeks PMA)	4	3.14	6	2.32	0.76
6.	Composite adverse outcome (any of the above 5)	28	22.04	59	22.86	0.51

Table 2: Major morbidities and mortality in infants born from ART and non-ART

S. No	Outcomes	ART		Non-ART		p-value
		n=127	%	n=258	%	
1.	Any grade IVH	29	22.83	73	28.29	0.313
2.	Culture positive sepsis	31	24.40	69	26.74	0.07
3.	NEC stage 2A or more	9	7.08	21	8.13	0.16
4.	PDA-surgical ligation	3	2.36	2	0.77	0.1
5.	Hs-PDA requiring treatment	33	25.98	66	25.81	<b>0.03</b>
6.	>28 days oxygen need	22	17.32	39	15.11	0.63
7.	Respiratory support duration (Invasive)	0 (0-2)		0 (0-2)		0.44
8.	Respiratory support duration (total)	6 (2-16)		7 (3-15)		0.94
9.	Surfactant	82	64.56	165	63.95	0.08
10.	RDS	86	67.71	174	67.44	0.12
11.	EUGR	109	85.82	164	63.56	0.67
12.	Discharge weight (grams)	1522 (1422-1662)		1480 (1420-1620)		0.37
13.	Discharge PMA (weeks)	17	13.38	17	6.58	0.54
14.	Any ROP	11	8.66	32	12.40	0.18

Table 3: Outcomes in infants born from ART and non-ART