

# Immediate neonatal outcome born after artificial reproduction technique : A matched control study

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## ABSTRACT

**Introduction:** Recent technologic advances have facilitated the fertility of sterile couples. Routine techniques frequently used in India are: in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI). The outcome of these pregnancies is controversial, according to numerous reports. Prematurity, low birth weight (LBW) and multifetal pregnancies seem to be more frequent in some studies, but others do not confirm this result thoroughly.

**Aims & Objectives:** To study the immediate neonatal outcome in infants born after artificial reproduction techniques (ART) when compared to that of infants born after natural conception of similar gestational age.

**Materials & Methods:** It is a prospective cohort study done at Neonatology division, Dr.Mehta's children hospital, Chennai for 2 years. Cases (ART conception group) - all infants born after IVF including inborn and infants referred to our hospital. Controls (spontaneous conception group) - infants born after natural conception of similar gestational age and with similar mother's age including inborn and infants referred to our hospital. Total of 60 cases and 60 controls were studied.

**Results:** Total number of admissions during 2 years study period were 1652 and among these 60 (3.7%) infants born after ART conception and 1592 (96.3%) were born after spontaneous conception. ART conception group, 18 (30.0%) were term infants and 42 (70.0%) were preterm.

**Conclusion:** Immediate neonatal outcomes like respiratory morbidities, CNS morbidities, mortality rate and duration of hospital stay in infants of ART group were comparable with infants of spontaneous conception group when gestational age and maternal age were matched. Artificial Reproduction Techniques per se did not influence the mortality of infants.

**Keywords:** Artificial Reproduction Techniques, mortality, maternal age

## INTRODUCTION

Recent technologic advances have facilitated the fertility of sterile couples. Such interventions come with a high costs. Annually, about one million babies are born by assisted reproductive methods throughout the world. Recently, numerous fertility clinics in our country give infertile couples a chance to become parents. Routine techniques frequently used in India are: in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI). The outcome of these pregnancies is controversial, according to numerous reports. Prematurity, low birth weight (LBW) and multifetal pregnancies seem to be more frequent in some studies, but others do not confirm this result thoroughly. In many developed countries, about 2 to 4% of all infants are born by IVF technique<sup>1</sup>.

The most important problems following assisted reproductive techniques are due to multifetal pregnancy, prematurity and LBW. According to studies by Wright and Kissin, 49 to 54% of assisted reproductive techniques (ART) pregnancy products are multifetal<sup>2-5</sup>. This rate is significantly higher than normal conceptions (about 3%). Multifetal gestation will bear a higher rate of morbidity and mortality for both mothers and infants. LBW, prematurity, neonatal and congenital malformations as well as sickness are more prevalent among these infants. Bergh, Friedler and Kallen, regarding LBW and neonatal mortality in some Asian and European countries, have reported a four to five-fold increase in IVF neonates as compared with the general population

## MATERIALS & METHODS

In all the study population ( cases and controls ) maternal demographic details, antenatal problems and treatment details, antenatal scan details, birth details (gestational age at delivery, mode of delivery, birth weight), resuscitation details, reason for NICU admission, physical findings, course in NICU, duration of hospital stay, investigations, details of treatment and neonatal outcome was noted. On admission all the vital parameters, general physical examination and a detailed systemic examination was done as per the proforma and the details recorded.

Demographic details like birth weight and gestational age, risk factors like antenatal insults, Apgar status and resuscitative problems were recorded and compared between the various groups. The incidence of short term morbidities like the presence of Respiratory distress syndrome requiring surfactant, hemodynamically significant PDA were noted. Intra ventricular hemorrhage, hyperbilirubinemia, renal failure and neonatal necrotizing enterocolitis were studied in various groups.

Gestational age at delivery in IVF(ART) pregnancies was defined as the difference between the date of oocyte puncture and the date of delivery with 14 days added. In control pregnancies gestational age at delivery was defined as the number of days between the date of delivery and the date of first day of LMP.

Preterm delivery was defined as a delivery before 37 completed weeks. Small for gestational age (SGA) was defined as a birth weight below the 10<sup>th</sup> percentile and Large for gestational age (LGA) was defined as birth weight above the 90<sup>th</sup> percentile. Low birth weight (LBW) was defined as a birth weight between 500 and 2500gm. Neonatal death was defined as the death of a liveborn infant of >=500gm during the first 28 days of life. Perinatal mortality was defined as sum of stillbirths and neonatal deaths, divided by the total number of live and stillbirths. A caesarean section called elective if performed before the onset of labour, otherwise it was classified as an emergency caesarean section.

**Statistical tests**

Statistical analysis was done using SPSS 16. Measures of central tendency and measures of dispersion were used to study the data distribution. Paired T test was done to compare means between 2 groups. For the same, McNemar test and McNemar Bowker test were carried out to compare categorical data of the groups.

**RESULTS**

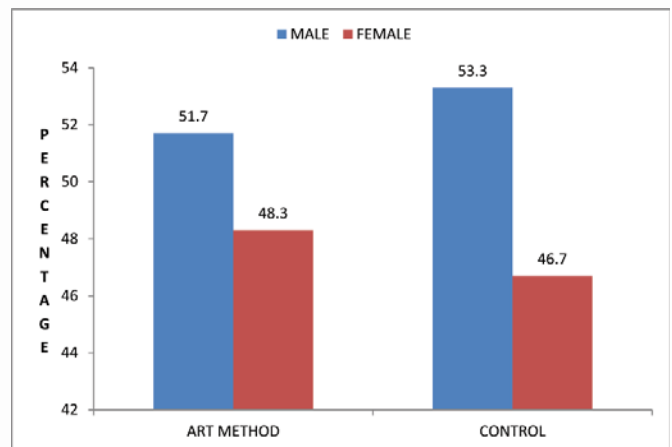
Total number of admissions during 2 years study period were 1652 and among these 60 (3.7%) infants born after ART conception and 1592 (96.3%) were born after spontaneous conception. In 1592 infants of spontaneous conception, 742 (46.6%) were term infants and 850 (53.4%) were preterm infants. whereas in ART conception group, 18 (30.0%) were term infants and 42 (70.0%) were preterm. Difference was statistically significant (p=0.011). [Table 1].

**Table 1: Gestational age distribution in admitted infants including spontaneous conception and ART conception**

Parameter	Spontaneous conception (N=1592)	ART (IVF/ICSI) conception (N=60)	P value
	742 (46.6%)		0.011
	850 (53.4%)		
	1546 (97.1%)		0.000
	40 (2.5%) (20 deliveries)		
	6 (0.4%) (2 deliveries)		

In all the four cases of dental ulcers, sharp teeth were seen adjacent to the ulcers. Removal of the sharp tooth was followed by complete healing of the ulcer. Among the 100 cases there were 8 cases of oral malignancy.

**quamous cell carcinoma was the most common his**



**Table 2 :Birth weight distribution in study group**

Birth weight	Group		Total	P value
	ART (n=60)	Controls (n=60)		
= 1000gms	5 (8.3%)	4 (6.7%)	9 (7.5%)	0.698
1000-1500gms	14 (23.3%)	15 (25.0%)	29 (24.2%)	
1500-2500gms	7 (11.7%)	7 (11.7%)	14 (11.7%)	
2500-4000gms	34 (56.7%)	32 (53.3%)	66 (55.0%)	
> 4000gms	0	2 (3.3%)	2 (1.7%)	

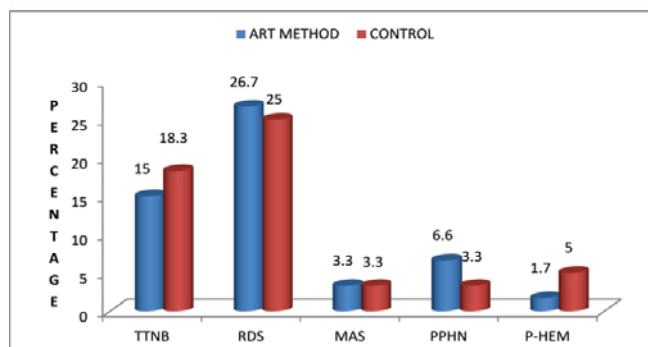
Extremely low birth weight (<1000gm) category consisted of 5(8.3%) babies in ART group and 4(6.7%) babies in control group. 1000-1500gm weight category comprised 14(23.3%) in ART group and 15(25.0%) babies in control group. 1500-2500gm weight category comprised 7 (11.7%) babies in each group. 2500 – 4000gm group contains 34 (56.7%) babies in ART group and 32 (53.3%) babies in control group. 2 (3.3%) infants with weight >4000gm were found in controls only [Table 2]. However there was no statistical difference between the groups in any of the birth weight ranges (p=0.698). Low APGAR score of <6 at 5 min was found in 3.3% of ART group and 5.0% of control group. Intubation during resuscitation was required in 3.3% of ART group and 5.0% of control group. Those infants just required bag and mask ventilation and improved with APGAR score =6 are not depicted here [Table 3].

In our study, the incidence of respiratory problems like Transient tachypnea of newborn (TTN) (15.0% Vs 18.3%), Respiratory distress syndrome (RDS) ( 26.7% Vs 25.0%), MAS (3.3% Vs 3.3%), PPHN (6.6% Vs 3.3%), apnea (11.7% Vs 13.3%), pulmonary hemorrhage (1.7% Vs 5.0%) and pneumonia (1.7% Vs 1.7%) were comparable between ART group and controls. Surfactant requirement for RDS was not statistically significant between ART group (26.7%) and controls(23.3%)(p=0.751) [Figure 2]. The incidence of GI system problems like feed intolerance, GERD, NEC, and G.I. tract anomalies were comparable between the study groups.

**Table 3 : APGAR status between the groups**

Parameter	Group		P value McNemar test
	ART (n=60)	Controls (n=60)	
Low APGAR (<6 at 5 min)	2 (3.3%)	3 (5.0%)	1.00
Intubation at resuscitation	2 (3.3%)	3 (5.0%)	1.00

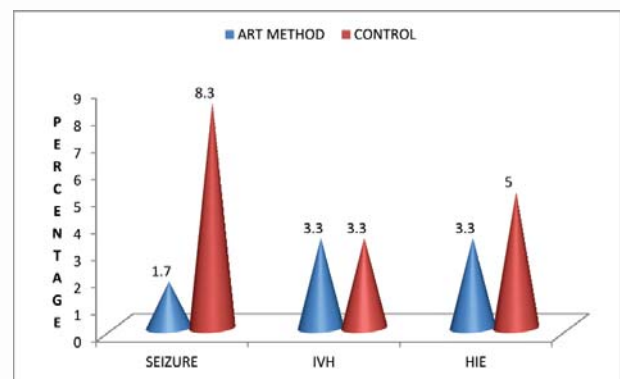
**Figure 2: Respiratory morbidities in study group**



Transient tachypnea of newborn (TTN) was found in 9(15.0%) infants in ART group and 11(18.3%) infants in control group. Respiratory distress syndrome (RDS) was found in 16(26.7%) infants of ART group and in all those 16(26.7%) surfactant was given whereas in controls, out of 15(25.0%) infants of RDS, 14 (23.3%) had received surfactant. Respiratory morbidities were not significant between the groups.

Though incidence of seizures was more in control group [ 5 infants (8.3%)] when compared to cases [3 infants (5.0%)], difference was not statistically significant (p=0.388). Hypoxic ischaemic encephalopathy (HIE) and Intraventricular hemorrhage (IVH) did not have any statistical difference between the groups(p=1.00) [Figure 3].

**Figure 3: Central nervous system morbidities in the study group**



**Table 4: Hyperbilirubinemia in the study group**

Jaundice	Group		P value McNemar Bowker test
	ART (n=60)	Controls (n=60)	
Mild	13(21.7%)	10(16.7%)	0.004
Moderate	6 (10.0%)	21(35.0%)	
Severe	2 (3.3%)	1 (1.7%)	

Mild hyperbilirubinemia was found in 13(21.7%) babies in ART group and in 10(16.7%) babies of control group. Moderate hyperbilirubinemia was found in 6(10.0%) babies in ART group and 21(35.0%) babies of control group. Severe hyperbilirubinemia was found in 2(3.3%) babies in ART group and in 1(1.7%) baby of control group. There is significant difference in the moderate hyperbilirubinemia category ( P value 0.004). None of the infants required exchange transfusion [Table 4]. Mean duration of hospital stay was slightly longer in ART group 12.3±11.8 days when compared to control group 10.8±9.0 days but it was not statistically significant [Table 5]. There is no significant difference between two groups with respect to mortality rate 4 (6.6%) infants died in ART group whereas in control group 5 (8.3%) infants died [Table 6].

Table 5 : Duration of hospital stay of infants in the study group

Parameter	Controls		N	ART Group		95% C.I		p value
	MEAN	SD		MEAN	SD	LOWER	UPPER	
STAY_DAYS	10.87	9.097		12.3	11.864	-3.556	0.689	0.182c

Table 6: Mortality rate and etiology of death in the study group

Parameter	ART		Controls	P value
Mortality	4(6.6%)	60	5 (8.3%)	P=1.00
<b>Cause for death</b>				
Extreme preterm/ sepsis/IVH	1 (1.7%) (one of twin)		2 (3.3%) (one of separate twins)	
CDH with severe PPHN	1 (1.7%) (singleton)		1 (1.7%) (singleton)	
VLBW/meconium ileus/IVH	1 (1.7%) (singleton)		0	
Extreme preterm/ sepsis/ pulmonary hemorrhage	1 (1.7%) (one of twin)		0	
Congenital myopathy with short limbs	0		1 (1.7%) (singleton)	
MAS with renal failure	0		1 (1.7%) (singleton)	

## DISCUSSION

In 1592 infants of spontaneous conception, 742 (46.6%) were term infants and 850 (53.4%) were preterm infants. Whereas in ART conception group, 18 (30.0%) were term infants and 42 (70.0%) were preterm. Difference was statistically significant ( $p=0.011$ ).

Singleton pregnancy (97.1%) was significantly higher in spontaneous conception group and Twin pregnancy (43.4%) was significantly higher in ART conception group ( $p=0.000$ ). 60 infants of spontaneous conception were taken as controls after completing matching criteria and are compared with the cases (ART conception group). In our study, we used two confounding factors for matching i.e. maternal age and gestational age.

In our study, 70% were preterm in ART conception group and 53.4% in spontaneous conception group. In our study, infants with birth weight <2500gm were 26 (43.3%) in ART group as well as control group.

In our study, elective LSCS (38.3%) and emergency LSCS (51.7%) were significantly higher when compared to

spontaneous vaginal delivery (10.0%) ( $p=0.00$ ) in ART group. In control group, vaginal delivery (30.0%) and elective LSCS (45.0%) were significantly higher ( $p=0.00$ ).

In our study, incidence of low APGAR score (<6 at 5 min) and need for intubation at birth were comparable between the groups (3.3% vs 5.0%  $P=1.00$ ). Koivurova et al 2002<sup>11</sup> reported that APGAR < 6 at 5 min was 3.4% in singletons and 7.9% in twins whereas in matched controls it was 7.5% and 9.0% respectively which was not significant. J.Koudstaal et al 2000<sup>12</sup> reported that no difference in the APGAR <6 at 5 min between ART group and controls.

In our study, the incidence of respiratory problems like TTN (15.0% Vs 18.3%), RDS (26.7% Vs 25.0%), MAS (3.3% Vs 3.3%), PPHN (6.6% Vs 3.3%), apnea (11.7% Vs 13.3%), pulmonary hemorrhage (1.7% Vs 5.0%) and pneumonia (1.7% Vs 1.7%) were comparable between ART group and controls. Surfactant requirement for RDS was not statistically significant between ART group (26.7%) and controls (23.3%) ( $p=0.751$ ).

CNS related morbidities: Though incidence of seizures was more in control group (8.3%) when compared to ART group (1.7%), difference was not statistically significant. Incidence of

intraventricular hemorrhage (3.3% vs 3.3%) and moderate to severe hypoxic ischaemic encephalopathy (3.3% vs 5.0%) were comparable between the two groups. In our study, the incidence of moderate hyperbilirubinemia was higher in controls (35.0%) than in ART group (10.0%) which was statistically significant ( $p=0.004$ ) and hence duration of phototherapy was also significantly longer in control group [ $p=0.00$  paired t test]. Cause of hyperbilirubinemia is multifactorial and other risk factors for hyperbilirubinemia were not studied. Hence reason for higher incidence of moderate hyperbilirubinemia in control group could not be derived.

In our study, mean duration of hospital stay was slightly longer in ART group ( $12.3 \pm 11.86$  days) when compared to that of controls ( $10.87 \pm 9.09$  days). Difference was not statistically significant.

In our study, there is no significant difference between two groups with respect to mortality rate. 4 (6.6%) infants died in ART group whereas in control group 5 (8.3%) infants died. 2 (3.3%) infants died of extreme prematurity and sepsis and grade 4 intraventricular hemorrhage in control group and 1 (1.7%) infant in ART group. 1 infant with CDH and severe PPHN died in each group. MAS with renal failure was reason for death in term baby in control group. Congenital myopathy was the reason for death in 1 infant of control group. 1 infant VLBW with meconium ileus and 1 infant of extreme prematurity with pulmonary hemorrhage died in the ART group.

#### CONCLUSION

Immediate neonatal outcomes like respiratory morbidities, CNS morbidities, mortality rate and duration of hospital stay in infants of ART group were comparable with infants of spontaneous conception group when gestational age and maternal age were matched. Artificial Reproduction Techniques per se did not influence the mortality of infants.

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