

Long Term Outcomes of Children Born by ICSI in Comparison to Spontaneously Conceived Children: A Retrospective Observational Study

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Abstract: *There are several studies which support the finding that Assisted Reproductive Technique (ART) is associated with adverse outcomes immediate neonatal period as well as later in the life of children born as a result of ICSI. Methodology: A retrospective observational study done among 50 babies born through ICSI from year 2008 to 2019 in Chettinad Hospital and Research Institute, Kelambakkam, who were followed up at baby meet clinic every year. Various parameters like mode of conception, antenatal, perinatal events were noted. Physical health, growth pattern and neuro developmental outcomes were studied and compared with spontaneously conceived children. Results: The chance of having a multiple pregnancy was found to be significantly higher in the women conceived by assisted reproductive techniques. Antenatal complications of PIH and GDM are found more commonly in women conceived by ICSI. Mean birth weight was more in children born out of natural conception. Overall in the long run children born of ICSI are significantly having a higher weight and height when compared to children who are born by natural conception. Developmental milestones were appropriate in both groups. Hearing and vision had no long term differences in both the groups. Conclusions: Contrary to the beliefs about the children born out of ART, it was observed that there was no significant difference in long term outcomes of children when compared to children born out of natural conception. So, by keeping this in mind, with a proper counselling and reassurance, ICSI can be preferred when a couple cannot conceive normally.*

Keywords: Assisted reproductive techniques, Intracytoplasmic sperm injection, natural conception, developmental outcomes

1. Introduction

ICSI (Intracytoplasmic Sperm injection) has been a widespread Assisted Reproduction Technique (ART), after its inception since 1991 by Palmero et al in Belgium. It is a most sought modality for the couples suffering with male infertility due to the concept of using single spermatozoon per oocyte. ICSI is a process in which it is possible even for azoospermic men to become genetic fathers of their offsprings but in comparison with IVF, ICSI is more invasive and bypasses the process of natural sperm selection.¹

As per various studies, concerns were expressed about the detrimental outcomes in terms of medical as well as developmental/psychological follow-up of these children, yielding mixed to reassuring findings regarding very young to school-aged ICSI children's motor and cognitive development if poor quality semen is used^{2,3}

Chief concerns are mainly in terms of potential changes in genetic material, the possible transmission of foreign genetic material, the use of immature or senescent germ cells and associations between genetic disorders and some forms of male infertility, various meta analyses have also supported the same finding.^{3,4,5}

The collection and interpretation of data from epidemiological studies of ART is challenging due to a lack of uniformity of clinical definitions and differences in data collection methods. Follow-up of both obstetric and child outcomes post-ART is crucial, particularly as new techniques are constantly being introduced. So, over the last few years, several follow-up studies were done on development of children born through ART especially ICSI in particular, especially long term and short term outcomes. This study as well will focus on summarizing the short- and

long-term health outcomes of children conceived using ART.

Aim & Objectives

To assess the health and developmental outcomes of children conceived by ICSI in comparison with spontaneously conceived children.

2. Methodology

This study was carried out in Chettinad Hospital and Research Institute, Kelambakkam. A written informed consent was taken from all the parents who were willing to participate in the study after discussing in detail about the need and objective of the study.

Study design: It is a retrospective observational study

Study setting: Chettinad Hospital & Research Institute, Kelambakkam

Study population: Study was done among a convenient sample of 100 children, of whom 50 babies were born through ICSI and 50 children born from natural conception. The babies born through ICSI were delivered in our hospital from year 2008 to 2019, who were followed up at baby meet clinic every year.

Duration of study: 3 months (July 2019- September 2019)

Various parameters like mode of conception, antenatal, perinatal events were noted. Development was assessed using Trivandrum Developmental Screening Chart. Physical health, growth pattern and neuro developmental outcomes were studied & compared with spontaneously conceived children

3. Results

In the present study, it was observed that both the groups had no statistical difference in comparable with age and gender. Birth weight of babies born by natural conception were significantly higher when compared to babies born by IVF, but during the study it was observed that the average height and weight of babies born by ICSI was more when compared to babies born by natural conception and the difference observed was statistically significant. (Table 1)

The mean age of the children studied was 4.292 ± 2.74 years in natural conception and the mean age of children born out of ICSI is 4.54 ± 2.63 years and there was no statistically significant difference has been observed thus both the groups were comparable. (Table 1)

Table 1: Sociodemographic and Anthropometric Characteristics

	ICSI	Spontaneous conception	P-value
Consanguinity	Yes	5 (10%)	1.000
	No	45 (90%)	
Gender	Male	21 (42%)	0.316
	Female	29 (58%)	
No. of Offspring	Singleton	35 (70%)	0.0001
	Multiple	15 (30%)	
	Age (years)	4.54 ± 2.63	
Birth weight (kgs)	2.604 ± 0.635	2.877 ± 0.554	0.009
Present weight (kgs)	18.822 ± 8.276	15.664 ± 6.280	0.007
Length/Height (cms)	102 ± 20.18	98 ± 19.96	0.006

In the present study, among the women who have undergone ICSI, 12% had PIH, 24% had GDM and none had hypothyroidism. Whereas, in women who conceived naturally, 6% had PIH, 10% had GDM and 8% had hypothyroidism and thus there was a significant difference in the antenatal profile of woman who had ICSI in comparison to woman who conceived naturally.

Of the various antenatal conditions, over all 9 women (18%) had PIH of them 6 (12%) had ICSI and 17 (34%) had GDM, among them 12 (24%) had ICSI and 4 women (8%) had hypothyroidism and all have conceived naturally. A statistically significant difference has been observed and it was found the antenatal complications were more among women who have conceived through ICSI.

Majority of the women who had ICSI had undergone elective or emergency LSCS, whereas half the women who have undergone natural conception had NVD as well and thus a statistically difference has been observed in the mode of delivery opted out by women

Table 2: Antenatal Characteristics and Mode of Delivery

Characteristics		ICSI	Spontaneous conception	P value
Duration of pregnancy	Pre term	16 (32%)	4 (8%)	0.003*
	Term	34 (68%)	46 (92%)	
Mode of delivery	NVD	4 (8%)	23 (46%)	<0.0001*
	Emergency LSCS	20 (40%)	17 (34%)	
	Elective LSCS	26 (52%)	10 (20%)	

Antenatal complications	PIH	6 (12%)	3 (6%)	0.03*
	GDM	12 (24%)	5 (10%)	
	Hypothyroidism	0	4 (8%)	
	NIL	32 (64%)	38 (76%)	

In the present study, the difference in the post-natal complications of the children born out of natural conception in comparison to the babies born as a result of ICSI was not statistically significant.

No significant differences in the appearance of congenital anomalies have been found in between the groups. The congenital anomalies noted in both groups were mild and not lethal.

The developmental milestones were appropriate for age in both groups. The statistical differences in the developmental outcomes between two groups were insignificant.

No significant difference has been observed in terms of vision and hearing abnormalities across the groups. (Table 3)

Table 3: Postnatal Characteristics and Complications

Postnatal complication	ICSI	Spontaneous conception	P value	
Jaundice	12 (24%)	10 (20%)	0.415	
Sepsis	3 (6%)	0		
Seizure	1 (2%)	1 (2%)		
Asphyxia	4 (8%)	5 (10%)		
Nil	30 (60%)	34 (68%)		
Congenital anomaly	Anomalies	2 (4%)	1 (2%)	0.502
	No anomalies	48 (96%)	49 (98%)	
Milestones	Normal	50 (100%)	50 (100%)	1.000
	Delayed	0	0	
Vision	Normal	47 (94%)	49 (98%)	0.503
	Myopia	2 (4%)	1 (2%)	
	Astigmatism	1 (2%)	0	
Hearing	Normal	50 (100%)	50 (100%)	-

4. Discussion

Though assisted reproductive techniques stand as the most sought after methods to deal with infertility among couples, till date there have been many misconceptions about the health and developmental outcomes of the offsprings born out of ART.

In the present study it was observed that the chance of having a multiple pregnancy was more in women who conceived through ICSI when compared to spontaneous conceptions and this finding was observed in many other studies. This is probably because of simultaneous transfer of multiple embryos at the time of conception themselves.^{6,7}

In the study conducted by Basatemur et al., and many other studies, which are conducted as meta analysis have concluded that multiple pregnancy is an important risk factor observed among as the major predictor of adverse outcomes after ICSI. Here they have observed that the

singleton pregnancies attained a normal weight but the children born out of multiple pregnancies had birth weight <2.5 Kgs⁸

Many of the studies stated that the birth weight of the babies born out of ART was significantly lower than the children born out of natural conception and it was concluded in many studies that the normal birth weight seems to be achieved with a term gestation⁹ but such a difference in the birth weight of babies is mainly because of the occurrence of more pre term delivery in the ART cases. The similar finding of significant difference in the birth weight of ICSI conceived children and children who are conceived naturally and more occurrence of pre term labours in women who have undergone ART. Here one measure to be taken to avoid lower birth weight in babies born out of ART is to wait till term for them to deliver and more work should constantly be put up to know the underlying mechanisms for low birth weights.

In the study conducted by Neubourg et al.,¹⁰ they have observed that there was no significant difference in the weights of children born out of IVF vs children born out of natural conception when the timing of birth was matched.^{7,11}

Though there was an initial difference in the birth weight of the babies in the later stages the weight was caught up and the similar observation was made in the study done by Bergh C et al.,¹² Bonduelle M et al.,¹³ and many others.^{14,15}

The birth weight of the children born out of ICSI was significantly lower than the children born out of spontaneous conception and this finding was in concordance with the study done by Miles¹⁶ and Green et al.,¹⁷

The antenatal complications of GDM and PIH are more in women conceived of ICSI and the chances of pre term births and LSCS were also more and the similar finding has been made in many studies. In the study conducted by Kjellberg et al.,¹⁸ they have demonstrated that significantly lower premature births and low-birth weights among the singleton pregnancies than multiple conceptions in ART. These various complications during antenatal and perinatal period in the mothers has been implicated to the various maternal parameters like age and various general parameters of the mothers.

However elimination of multiple pregnancies during ICSI may not completely eliminate adverse outcomes such as increased risk of preterm delivery, low birth weight, neonatal mortality, and neonatal intensive care unit admission in the perinatal period as supported by many meta-analysis^{19,20,21}

Coming to the post-natal complications, neonatal jaundice was more in children born out of spontaneous conception and rest of the parameters stand comparable. The developmental milestones were appropriate for age in both groups. Development of special senses did not show any long term difference when compared across children born out of ICSI and spontaneous conception and these findings are supported by various meta-analysis done on similar studies.^{22,23}

5. Conclusions

The present studies as well as many other follow up studies of offsprings born out of ICSI, it was observed that majority of the children born out of ICSI were healthy and the short term and long term outcomes were comparable with children born out of spontaneous conception. The main step to be taken to avoid low birth weight is to maintain the pregnancy till term and periodic scans to be done to establish a proper growth of the children. The main problem of low birth weight of children is mainly because of multiple pregnancies, which can't be predicted and thus it is needed to have a constant evaluation throughout the pregnancy for the proper growth of foetus. With an increasing tendency towards single embryo transfer, long term outcomes of the ART pregnancy must be educated to the couple for the best outcomes.

6. Limitations of the study

There could be possible confounding factors which needs to be elicited and further larger studies are to be done.

7. Conflicts of interest

Nil

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