Original Article

Follow up of ART Babies

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Abstract

Assisted reproductive technology (ART) has been accepted as a viable and safe method of treatment for infertile couples. Although a number of studies have been reassuring, there still remains concern about poor perinatal outcomes & congenital anomalies in the babies born. Very few Indian studies on the follow up of ART babies have been reported. Our study evaluates the outcome of babies born as a result of ART treatment at the Department of Reproductive Medicine at Chettinad Medical college and Research Institute, Kelambakkam, Tamil Nadu. A total of 123 babies were included in our 5 years follow up study. The growth mile stones and cognitive development were assessed through personal check up, telephone calls and emails. Congenital anomalies observed in our study were 4%. None of the anomalies could be attributed directly to ART. Growth and development were normal for all these babies. However further long term follow up and comparison with naturally conceived babies during the same period is required to ensure the safety of these advanced techniques.

Key Words: ICSI, Follow up, ART babies, Anomalies

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Introduction

Ever since the world's first IVF baby was born in the year 1978[1], there has been a phenomenal growth in the use of A.R.T for the treatment of the infertile couples. Although a large number of studies on the health of babies born using ART have been reassuring[1], no published data exists for the Indian scenario. The Department of Reproductive Medicine at Chettinad Hospitals has strived to conduct a study on the health and well-being of babies born using ART.

Aim of the Study

To assess the well-being of babies born out of IVF/ICSI from Chettinad Health City from March 2008 to April 2014, and to establish the incidence of congenital anomalies in these babies.

Materials & Methods

Babies born either by fresh or frozen embryo transfers as a result of IVF and ICSI treatment in the Department of Reproductive Medicine Chettinad Health City, from March 2008 to April 2014 were included in this study. The babies were individually assessed by a program called "Babies Meet", which is conducted annually. Details from parents regarding antenatal events such as Pregnancy induced hypertension (PIH), Gestational diabetes mellitus (GDM), Ante-partum haemorrhage (APH), History of preterm labour and Premature rupture of membranes (PROM) and use of any medications during pregnancy were collected retrospectively. The perinatal events, mode of delivery, indications for LSCS were also noted. Birth weight, APGAR (1 min and 5 min), NICU admissions and its progress, breast feeding history were recorded.

Clinical follow up of children through the event "Babies Meet"

Babies were examined by a team of Paediatricians. Morphometric features (weight, height) and mile stones were checked. Cognitive function, behaviour were also assessed. Any anomalies observed were also noted. Individual case records were prepared by Paediatricians.

Follow up through phone call

Some children who could not come for the paediatric assessment for personal reasons and who resided out of station/country were followed up by phone calls and e-mails. Parents were requested to provide a paediatric assessment of their children and follow up details were recorded. Periodic phone calls were made to follow up the milestones.

Results

Total number of pregnancies following A.R.T were 221. Of these 111 mothers delivered. All the observations are presented here in tables 1-11.

Pregnancy Outcome - Distribution

Table 1

PREGNANCY OUTCOME	NUMBER OF PATIENTS	PERCENT--AGE
Biochemical pregnancy	35	15.8%
Ectopic Pregnancy	5	2.2%
Spontaneous miscarriage	24	10.8%
Missed miscarriage	14	6.3%
Molar pregnancy	1	0.4%
Ongoing pregnancies	31	14%
Total number delivered	111	50.2%
Total number of pregnancies	221	

Means of follow up

Table 2

FOLLOW UP	NO.TRACED
Total number of deliveries	111
By babies meet	40 (36%)
By phone call	59 (53.1%)
Not traceable	12 (10.8%)

Out of 221, only 111 pregnancies ended up in live births. Among the 111, details of 99 could be traced and the rest (12) were lost for follow up. There were 75 singletons and 24 twins born of 99 deliveries. So the total number of babies on our follow up was 123. There were 3 triplets reduced to twins. 75 mothers could reach the full term before delivery and 24 mothers delivered pre term babies.

Parental Age

Table 3

AGE	MOTHER	FATHER
20-29	33 (33.3%)	6 (6%)
30-39	62 (62.6%)	75 (75.7%)
40 and above	4 (4%)	18 (18.1%)
Total	99	99

Majority of parents were in the age group 30-39 years.

Indications for A.R.T

The indications requiring ART treatment are presented in Table 4.

Table 4

INDICATION FOR A.R.T	NO OF CASES	PERCENTAGE (%)
Male factor	28	28.2%
Female factor	38	38.3%
Unexplained	24	24.2%
Combined	9	9%
Total	99	

Table 5

ANTENATAL COMPLICATIONS	NO OF PATIENTS
GDM	10
Placenta praevia	1
Oligohydramnios	3
PIH	6
GDM and PIH	2
PROM	1
Triplet reduction to twins	3
Total	26 (26.2%)

Of 99 mothers only 26 mothers had antenatal complications. GDM was the most frequently observed complication in our study group, followed by PIH. GDM was prevalent in female factor infertility. Out of 12 patients with GDM, 3 mothers had polycystic ovarian syndrome.

Table 6

AGE VS Complication	20-29 yrs	30 - 39 yrs	>40 yrs.
Placenta previa	1	Nil	Nil
Oligohydramnios	-	3	Nil
GDM	2	6	2
PIH	1	5	Nil
GDM & PIH	1	1	Nil
PROM	-	1	Nil

Antenatal complications were more common in mothers between 30- 39 yrs of age, there were 4 mothers above 40 yrs of age & 2 of them had antenatal complications (GDM).

Mode of Delivery

Table 7

MODE OF DELIVERY	NO OF DELIVERIES	PERCENTAGE
Normal vaginal	7	7.07%
LSCS	92 (33+59)	92.9%
Total	99	

Majority of patients underwent LSCS, of which 59 were elective and 33 emergency.

Weight of the babies at birth

Table 8

WEIGHT	SINGLE	TWINS	PERCENTAGE
<2KG	4 (preterm)	13 (preterm)	13.8%
2.1-3.0KG	52 (8 preterm)	35 (4preterm)	70.7%
>3.1KG	19	-	15.4%
Total	75	48	

NICU treatment

Table 9

INDICATIONS FOR NICU ADMISSION	NO.OF BABIES
Low birth weight	3
Jaundice	5
Preterm	7
Respiratory distress	4
Hypoglycaemia	1
Observation	8
Total	28 (22.7%)

Age of Babies at the Time of Follow Up

Table 10

AGE IN MONTHS	NO OF BABIES	PERCENTAGE (%)
Less than 12	33	33.3%
13-24	22	22.2%
25-36	13	13.1%
37-48	23	23.2%
49-60	8	8%

Oldest baby at follow up was 5 years old. Out of 77 singletons, 33 were male babies and 44 were female babies. Of 46 twin babies, 22 were male and 24 were female babies. There were no known identical twins.

Congenital Anomalies

Table 11

CONGENITAL ANOMALIES	NO OF BABIES	FOLLOW UP
Ovarian cyst	1	Operated
Meningo-myelocoele	1	Expired
Congenital talipes equino varus	2	1-corrected 1-on treatment
Patent foramen ovale	1	On treatment
Total	5 (4%)	

There were 5 babies with congenital anomalies. 2 had congenital talipes equino varus, 1 had ovarian cyst, 1 Meningo-myelocoele, 1 baby had patent foramen ovale. One baby on follow up had an acquired complication of meningitis (normal at birth) at 3 months of age and the baby expired despite treatment.

Discussion

The majority of the women in our study had an uneventful antenatal period. GDM was the most commonly observed medical complication (Table 5). However, mothers more than 30 years of age demonstrated antenatal complications like GDM, PIH, PROM and had an association with the duration of infertility (Table 6). The deliveries were conducted by the Obstetricians who had referred the patients and not by the Reproductive Medicine Specialists in the department. Considering the fact that 75 were singleton pregnancies, the high rate of operative deliveries (92/99) indicates the anxiety of the couples and the care given in dealing with the IVF-ICSI pregnancies.

The birth defects reviewed by Wen et al., 2012 (who had reviewed 46 studies containing 124468 IVF/ICSI children), reported a 2.01% defects for nervous system followed by 1.69% for genitourinary, 1.66% for digestive system, 1.64% for circulatory system, 1.48% for musculoskeletal system and 1.43% for eye, ear, face and neck[1]. The incidence of congenital anomalies in our group is 4%, comparable to naturally conceived children in Indian population 2-3% [2].

Out of the 5 anomalous children (table 11), 2 had CTEV. The reported incidence of CTEV in ICSI babies is 1.48% and in general population is 1-2/1000 live birth[3]. The commonest associated factor is intrauterine compression to fetal parts due to Oligohydramnios / amniotic bands or crowding of fetal parts due to multiple pregnancy[3]. Most of the CTEV are sporadic but in few situations like Edwards syndrome, Ehlers-Danlos syndrome and Loeys-Dietz syndrome it is familial[3]. Because one of the CTEV babies was one of the twins, this could be the contributing factor. The other did not show any associated factors as mentioned above and we conclude that it is sporadic.

Ovarian cysts are estimated to be present in 30% of foetuses and an increase in detection could be attributed to the widespread use of prenatal ultrasound[4]. The fetal and neonatal ovarian cyst are most likely caused by endogenous hormonal stimulation such as fetal gonadotropin, maternal estrogens and placental HCG[5]. Also an association with maternal diabetes, fetal hypothyroidism and fetal ovarian cyst has been observed in certain studies[4,6]. Because after birth the estrogens and HCG decreases rapidly, spontaneous resolution during the neonatal period is seen in most cases[5]. Our baby with the ovarian cyst was born to a mother with GDM and PIH and showed a complex cyst diagnosed at 36 weeks of intrauterine life and persisted till 3 months after birth. As it did not show signs of spontaneous regression it was surgically excised as per the standard recommendations[4] and was found to be benign in nature.

One female child with Meningo-myelocoele died 4 days after birth which was one of the twin babies. Other twin was a male baby and is healthy. Although the exact etiology of Meningo-myelocoele has not been established so far, deficiency of folic acid in women during the early pregnancy is known to be the most important cause[2]. All of the patients in our study were prescribed periconceptional folates and remained compliant with the medication. It is therefore highly unlikely to be the cause for this defect. The most commonly reported complication of cerebral palsy[1,6], was not seen in our cohort of babies.

The baby with patent foramen ovale was one of the twins born to a hypertensive mother at 35 weeks gestational age for uncontrolled hypertension. The incidence of cardiovascular anomalies in ART children is 1.64%[1,6] and the incidence in general population in India is about 2 per 1000 live births.

Twenty eight patients in the study group had male factor infertility. Azoospermia was present in 8 men & oligoasthenoteratozoospermia (OATS) in 20 men.

Although ICSI for severe male factor is associated with increased incidence of genito-urinary abnormalities,[1,6] in our study we have had no urogenital malformations for severe male factor. Because the acceptance for karyotyping and Y-chromosomal deletion studies prior to ART in this group of men is poor or non-existing, it is difficult to associate the possibility of any chromosomal defects in these men.

Several contradicting studies on cognitive and motor development in children of different age groups conceived through ICSI exist. Leunens and Zing[7] in 2006 compared 86 ICSI and 165 IVF conceived children of 4-6 years of age and found no significant difference between the ART group and natural conception group. Bonduelle[8] used Bayley test in children <2 years to assess the psychomotor development and found that the ICSI children were normal and comparable with the natural conception group. However Heineman[9] found the prevalence of autism, autism spectrum disorder to be higher after ICSI. Autism spectrum disorders are a group of neuro behavioural disorders that are marked by social and communication deficit, including repetitive stereotypic behaviour. On the contrary, large study in Denmark by Hvidtjorn[10] between Jan 1995 to Dec 2003 found no increased risk.

Most of our ART children were examined by Paediatricians during our "Babies Meet" for communication skills, work skills, socialization, speech, fine motor development etc. All these babies were found to be normal. The younger babies who are <3 years old were examined for mile stones, speech and were found to be comparable with the natural conception group. Even the behaviour of the children was assessed meticulously and found to be normal so far. The rest was traced through phone calls and e mails to the parents and their well being recorded.

There is always a fear of getting some epigenetic imprinting disorders due to some potential mechanisms by which ART could contribute to the creation of epimutations[11]. The composition of culture media, environment, disruption of maternally imprinted genes with super ovulation, hypomethylation of paternal and maternal genes and the underlying condition of infertility itself could all be associated with imprinting abnormalities. The actual risk for one of the imprinting phenotypes (Silver - Russell syndrome, Beckwith-Wiedemann syndrome, or Angelman syndrome) to occur in an assisted pregnancy is estimated to be low, at less than 1 in 5000[6]. The exact etiology for this imprinting disorder is likely to be heterogeneous and requires more research. We had no child with features suggestive of epigenetic disorders in our series.

Our stringent policy on number of embryos transferred has led to a minimal and acceptable multiple pregnancy rates. This has further limited the consequence of multiple pregnancies like increased incidence of PIH, PROM, prematurity, low birth weight and perinatal complications. Multi fetal reduction can be emotionally very difficult for couples who have conceived through fertility treatment, particularly when the procedure results in the loss of entire pregnancy[12]. We had only 3 patients for whom triplets were reduced to twins and these three patients delivered normal babies.

Conclusion

The observations of babies born in our ART study group have been reassuring and conform with the finding in natural pregnancies in terms of congenital anomalies, growth and development till 5 years of age. The commonly reported genitourinary anomalies in children born after ICSI for severe male factor were not seen. The other anomalies which were seen did not show a positive correlation with ART conception and majority were correctable. Because the number of patients in our study was small, a longer follow up with a larger group is required for confirming the safety of the babies born out of ART.

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