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Original Research Article

A study of various neonatal outcomes and complications in live-born infants among IVF pregnancies

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ABSTRACT

Background: In-vitro fertilization or Assisted reproductive techniques (ART) is the most advanced technique of infertility treatment. In-vitro fertilization (IVF) has helped couples all over the world. However, the use of IVF has raised significant concern about the outcome of resulting pregnancies and the health of the newborns. There is a range of possible factors associated with the treatment that may contribute to potential adverse outcomes. Thus, the study was conducted to analyze the neonatal outcomes of children born by ART in the Indian context.

Methods: The neonatal characteristics and complications of the live-born infants through IVF at Army Hospital R and R were analyzed in this study between March 2019 to February 2020.

Results: Total 231 babies were born to the study group cases. 126 (54.54%) were singletons, 102 (44.16%) were of twin pregnancies and 1.3% were triplets. There were 65.36% term and 34.63% preterm. Of the 231 IVF neonates, 58 needed neonatal intensive care. There were 219 (94.8%) survivors, while 12 (5.2%) did not survive a week. The 16 (6.92%) survivors needed readmissions mainly due to hyperbilirubinemia. There were 106 (45.8%) babies whose weight was less than 2 kg.

Conclusions: Infertility cases are usually older, and this is one reason for increased pregnancy and newborn infant complications. Neonates born through IVF appeared to be at higher risk of multiple births, prematurity, low birth weight, and other disabilities.

Keywords: Infertility, In-vitro fertilization, Low-birth weight, Neonates

INTRODUCTION

The World Health Organization (WHO) has made an estimate of 60 to 80 million couples worldwide currently suffer from infertility. The WHO estimates the overall prevalence of primary infertility in India to be between 3.9 and 16.8 percent.¹ Treatment options include Intra-uterine insemination (IUI), ovulation induction, IVF, ICSI, gamete intra-fallopian transfer (GIFT), zygote intra-fallopian transfer (ZIFT), cryopreserved embryo transfers and the use of donor oocytes. Since IVF has become an efficient and widely used treatment for infertile couples over the last 20 years, there has been focused analysis

about the health of children born after this treatment. Because of the relative novelty of IVF, the follow-up of children born after IVF is still quite limited. IVF is responsible for the increasing number of multifetal pregnancies, multiplicity being an important risk factor for adverse neonatal outcomes due to preterm birth, low birth weight and small for gestational age (SGA).²⁻⁶

A number of studies have shown, babies born after IVF have more neonatal problems and need longer hospitalization and intensive care than spontaneously conceived ones.^{4,7,8,9} Lancaster's study from the late 1980s was the first to report a higher prevalence of neural tube

defects and transposition of the great vessels among IVF children.¹⁰ The majority of later studies have been negative as far as congenital malformations are concerned. However, a few very recent studies have reported an increase in the prevalence of neural tube defects, oesophageal atresias omphalocele and hypospadias (after ICSI) among IVF children compared with spontaneously conceived controls.^{5,11}

The objective of this population-based study is to analyse neonatal outcomes, the need for hospitalization after birth and the prevalence of congenital malformations among IVF children.

METHODS

After the approval from the Ethics committee of our hospital (Army Hospital R and R), the present study was performed between March 2019 to February 2020. Of the total pregnant women who conceived through IVF, 200 pregnant women were taken to the study. The informed consent was taken from them. All patients were checked by a detailed history, clinical examination, and relevant investigations. After the enrolment, the patient was followed up closely throughout pregnancy, labor, and delivery, including the newborn baby's condition. Obstetrics outcomes in the women and the neonatal characteristics of the live-born infants were analyzed in this study. It is a prospective cohort study.

Inclusion criteria

Pregnant females conceived as a result of IVF. Neonate born as a result of IVF pregnancy.

Exclusion criteria

Pregnant females suffering from any disease before pregnancy. Pregnant females conceived spontaneously.

Statistical analysis

Data entry with the help of Microsoft Excel 2013 and statistical analysis were performed with the help of Statistical package for social sciences (SPSS) version 20.0, while categorical variables are presented as absolute numbers and percentages.

RESULTS

Since the study was observational, there were no control variables, and hence, the results were compared with the previous studies.

The patient's age profile varied from 23 to 41 years; there were 85 patients whose ages varied from 30 to 40 years. Infertility cases are usually older, and this is one of the reasons for increased complications in pregnancy. During the mentioned period, a total of 231 live neonates were delivered through IVF in 200 pregnancies. Neonatal

characteristics of live-born infants till 28 days of age were analyzed. Out of 231 neonates, 126 (54.54%) were singletons, 102 (44.16%) were products of twin pregnancies, and 3 (triplets) from one triplet pregnancy (1.3%). All were live births.

Table 1: Birth weights.

| Birth weight | Number |
|----------------|-------------------|
| Less than 1 kg | 23 (3 singletons) |
| 1-2 kg | 83 (3 singletons) |
| 2-3 kg | 100 |
| 3-4 kg | 25 |
| > 4kg | Nil |

Table 2: Neonatal Characteristics of IVF conceptions (n= 231).

| Characteristics | Number of neonates | % | Remarks |
|-----------------------------|--------------------|-------|---|
| Gestation | | | |
| Term | 151 | 65.36 | *Any infant <37 weeks (completed) gestation |
| Preterm* | 80 | 34.63 | |
| Weight for gestation | | | |
| Appropriate | 176 | 76.2 | |
| Small | 53 | 22.9 | |
| Large | 2 | 0.99 | |
| Sex | | | |
| Females | 112 | 46.87 | |
| Males | 119 | 53.13 | |
| Number | | | |
| Singletons | 126 | 54.54 | High twin incidence |
| Twins | 102 | 44.16 | iatrogenic |
| Triples | 3 | 1.3 | |

There were 112 (46.87%) females and 119 (53.13%) males in this cohort of IVF neonates. There were 151 (65.36%) term and 80 (34.63%) preterm. Most (176; 76.2%) were appropriate for gestational age, 22.9% (n=53) were small for gestational age while 2 (0.99%) neonates were large for gestational age.

The overall mean weight was 2.04 kg, the median weight 2.04 kg with the minimum being 0.5 kg and the maximum 4 kg. Low birth weight neonates (167/231) formed just above half the cohort (72.2%). There were only six singleton pregnancies where the weight was less than 2 kg depicted in Table 1.

More than half (127/231; 54.97%) of the neonates were delivered by lower segment caesarean section (LSCS), while 104 (45.02%) were delivered vaginally. Emergency LSCS was more common in singleton pregnancies (34/44; 77.27%), while elective LSCS was performed more frequently (34/35; 97.14%) in twin pregnancies. The

neonatal characteristics are depicted in Table 2. A total of 29 (12.5%) neonates needed some form of resuscitation at birth. Of the 231 IVF neonates, 58 (23.1%) needed neonatal intensive care. There were 219 (94.8%) survivors,

and of the 12 (5.2%) who died, 3 (25.0%) dies within the first 24 hours, 7 (58.3%) within seven days, and the other two (16.6%) not surviving the neonatal period.

Table 3: Congenital anomalies in IVF neonates (n=9).

| Number | Nature of anomaly | Mode of Diagnosis | Management | Remarks |
|--------|---------------------------|---|----------------------------------|--|
| 1 | Hirschsprung's disease | Contrast radiograph | Advised biopsy; refused | Died of acute colitis at 5 months of age |
| 1 | TGA with intact septum | Echocardiography | Initial PGE1 then surgery | Died on day 24 due to sepsis |
| 1 | Trisomy 21 | Karyotyping | On follow-up | On follow-up |
| 1 | Atrial septal defect | Echocardiography | On follow-up | On follow-up |
| 1 | Facial dysmorphism | Visual | All tests and karyotyping normal | On follow-up |
| 1 | Minor anomalies | Polydactyly 01; Preauricular tags 01; Partial Iris atrophy 01; Labial fusion 01; Large head 01 | On follow-up | On follow-up |
| 1 | Antenatal PUJ obstruction | USG; DTPA and GHA postnatally | Obstruction resolving | |
| 1 | Hypospadias | Visual | On follow-up | On follow-up |
| 1 | Stridor | Large thymic mass on imaging | Mass surgically removed | On follow-up |

Table 4: Readmissions during the neonatal period in IVF neonates (n=16).

| Number | Nature of morbidity | Day of life readmitted | Management | Remarks |
|--------|-----------------------------|------------------------|--|---|
| 4 | Neonatal hyperbilirubinemia | Day 3,4,5,6,7,8,9,15 | Phototherapy | All responded to phototherapy. |
| 2 | Sepsis | Days 8, 11, 14, 15, 17 | Antibiotics | One MSSA, others clinical sepsis |
| 2 | Feeding difficulties | Days 11, 13, 14 | Supervised breastfeeding | All improved |
| 1 | Aspiration Pneumonia | Days 25 | Antibiotics and chest physiotherapy | Improved |
| 1 | Seizure disorder | Day 8 | Phenobarbitone | Seizure free, off drugs, and development normal at seven months |
| 1 | Gastroesophageal reflux | Day 16 | Domperidone for one month, off drugs now | Radionuclide milk scan diagnosis |
| 1 | Hirschsprung's disease | Day 6 | Advised surgery | See the previous table |
| 1 | Biliary hypoplasia | Day 20 | Split liver transplant | Transplanted at 13 months |
| 1 | Pustular dermatitis | Day 5 | Antibiotics | Discharged |
| 1 | Dehydration fever | Day 5 | Supervised feeding. | Discharged |
| 1 | Hypoglycemia | Day 4 | Initial Infusion then supervised feeding | Due to faulty feeding |

The primary cause of death was as follows: Infection in 2/12 (16.6%), respiratory 6/12 (50%), cardiac anomaly in 1/12 (0.8%), and other systems in 3/12 (25%). The neonatal mortality rate (NMR) for the IVF neonates cohort was 51.9 per 1000 live births. Congenital anomalies were detected in 9 (3.89 %) of the cohort (Table 3).

A total of 16 (6.92%) neonates needed readmission within the neonatal period. All 16 neonates survived the neonatal period (Table 4). The 16 survivors needing readmissions were primarily due to hyperbilirubinemia 4/16 (25%) followed by sepsis (2/16) and feeding difficulties (2/16).

DISCUSSION

The present study was done to assess association of applications of ART with various neonatal outcomes. The most typical complication was multiple pregnancies along with other sequels. The incidence of twins was the highest.

During the period mentioned in the study, 231 live neonates were delivered as a result of IVF in 200 pregnancies. Neonatal characteristics of live-born infants till 28 days of age were analysed. Out of 231 neonates, 126 (54.54%) were singletons, 102 (44.16%) were products of twin pregnancies, and 03 (1.3%) were triplets. This compares well with the reported rates of 24.3% twin pregnancies from the Danish National IVF Registry, 46% from Manchester, 23% from the Bourn-Hallam Group and 44.5% from a large cohort of 31582 babies born in the years 1997-2000 after IVF.^{7,12-14}

There were 151 (65.36%) term and 80 (34.63%) preterm. IVF pregnancies are known to have higher rates of preterm deliveries, with various studies reporting rates of 23.8%, 34.9%, 25% and 29.4%.^{7,12,13,15,16} The higher rate of preterms in this study may be due to the higher prematurity incidence even in non-IVF births in our country. Low birth weight neonates (167/231) formed just above half the cohort (72.2%). The neonatal characteristics are depicted in Table 1. The percentage of low-birth-weight neonates is also high in IVF babies with reported rates of 23.6%, 43.2%, 32% and 20.5%. Our low-birth-weight rate of 48.1% compares well with the range across various studies.^{7,12,13,16}

The present study reports 22.9% of neonates to be small for gestational age, which also compares well with the 16.2% reported in a study of singleton neonates born following IVF.⁹ Another study has reported a double incidence of small for gestational age in IVF neonates than in non-IVF neonates.¹⁷

Of the 231 IVF neonates, 58 (23.1%) needed neonatal intensive care. There were 219 (94.8%) survivors and of the 12 (5.2%) who died, 3 (25.0%) dies within the first 24 hours, 7 (58.3%) within seven days, and the other 2 (16.6%) not surviving the neonatal period. The increased morbidity and need for intensive care amongst IVF neonates are well known, given the high-risk group they

belong to.^{7,18} Many studies report up to a twofold increase in mortality rates for IVF neonates.^{13,15,17}

Congenital anomalies were detected in 9 (3.89 %) of the cohort (Table 2), which is higher than the 2.5% reported in the Bourn Hallam group, but was lower than the 5.21%, 4.8% and 6.1% reported in other studies.^{7,13,12,17} Other than lower maternal age, we are not aware of any specific factor that could have led to these rates of congenital anomalies in our study.

The 16 (6.92%) survivors needing readmissions were mainly due to hyperbilirubinemia 4/16 (25%). In other studies, babies born by assisted reproductive technologies showed a 15 times higher risk of neonatal intensive care unit (NICU) admission. They were admitted primarily for supportive care for feeding initiation, a few developed complications like neonatal jaundice, neonatal sepsis, and difficult respiration. There was only one baby among 82 cases with multiple congenital malformations who did not survive even after resuscitation. Hansen et al. reported a 30–40% significantly increased risk of congenital disabilities among children born to ART-conceived women in a meta-analysis of 25 studies.¹⁹

Though increased maternal age and heightened anxiety levels amongst mothers of IVF neonates along with increased prematurity and low birth weight rates, do cause feeding difficulties, most can be overcome by good counselling and initial supervised feeding. It probably is reflected by the low rate of readmission for feeding difficulties in our study. We are aware that there are additional risks of developmental delay, increased hospitalizations and illnesses during the first 3 years of life amongst IVF babies as well as disorders due to abnormal imprinting 14 and therefore, follow-up of these infants is needed.^{14,15,18,20}

Limitations

Some of the outcomes could be influenced by maternal characteristics such as socioeconomic status and infertility diagnosis. Infertility diagnosis, the impact of different culture media, and the freezing method can be confounding variables that may affect neonatal outcomes. Furthermore, the pooling of reported IVF data creates a limitation in evaluating adverse neonatal outcomes based on the fertilization technique.

CONCLUSION

In conclusion, IVF neonates are at risk of multiple births, increased prematurity rates, and low birth weight with increased NMR, but the 94.8% survival rates in this study show the hope for the infertile couples who long for parenthood. Furthermore, there is a need for a large sample, multi-centric studies along with the controls to compare the results with pregnancies conceived spontaneously.

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