Profile of Live-born Infants of In-vitro Fertilisation

Surg Capt S Narayan*, Col KS Rana⁺, Col M Sharma[#], Col RK Sharma^{**}, Lt Col P Talwar⁺⁺,
Col K Kapur^{##}, Col BK Goyal^{***}

Abstract

Introduction: The Army Hospital (R&R) is the only service hospital providing in-vitro fertilisation (IVF) facility. Neonatal characteristics of live-born infants at this centre over a two-year period are analyzed in this study.

Methods: Data on 504 consecutive live-born IVF infants over a two-year period (01 Feb 2007 to 31 Jan 2009) were analysed.

Result: Of the 504 neonates, 190 (37.7%) were born by vaginal delivery, 156 (30.9%) by elective lower segment cesarean section (LSCS) and 127 (25.19%) following emergency LSCS. Maternal illness posing specific risk to the neonate was present in 165 out of 504 (32.7%). There were 239 (47.4%) preterm neonates. Males formed 51.8% of the cohort. Singletons accounted for 51.2%, while the rest (48.8%) were products of twin pregnancies. Small for gestational age neonates formed 22.6% (n = 114). A total of 20 (3.9%) infants had congenital malformations. There were 242 (48.1%) low birth weight neonates. A total of 128 (25.4%) neonates needed neonatal intensive care. Of the 504, there were 474 (94.1%) survivors while 30 (5.9%) did not survive. Twenty-nine (6.1%) neonates required readmission during the neonatal period.

Conclusion: In our setting, neonates born following IVF appeared to be at increased risk of prematurity, multiple births and low birth weight. Proper obstetric and neonatal management can result in good neonatal outcomes.

MJAFI 2010; 66 : 18-21

Key Words : In-vitro fertilisation ; Live-births; Low birth weight

Introduction

Advances in medical science, more specifically in-vitro fertilisation (IVF), have helped realize the dreams of parenthood of many infertile couples. With increasing numbers of infants born following IVF, a number of issues related to these infants have come to the fore in medical literature. These issues include increased infant mortality rates, failure to thrive, increased morbidity in early childhood [1], increased risk of congenital anomalies [2-4] and increased incidence of adverse neurological sequelae [5].

IVF is available in India for some time now but there are few reports on the neonatal outcomes of such conceptions. Against this background, this paper looks at the neonatal profile in live-births following IVF over a two year period in the Armed Forces.

Material and Methods

Data on all consecutive live births following IVF was prospectively collected from 01 Feb 2007 to 31 Jan 2009 (both dates inclusive) and analysed.

Parental characteristics studied included maternal age, type of infertility, maternal blood group and presence of maternal illnesses. The mode of delivery, indication for caesarean

section, need for resuscitation and birth weights of neonates were studied along with the presence of congenital anomalies and other morbidity. The need for intensive neonatal care, mortality and morbidity along with need for readmissions within the neonatal period were also studied. Standard, internationally accepted definitions for categorizing neonates were used.

All data was entered in an Excel spreadsheet and descriptive statistics used to analyse the data.

Results

During the two year period, a total of 1443 live neonates were delivered at our centre. Of these, 504 (34.9%) were products of IVF in 385 pregnancies. Out of 1443 neonates, 1144 (79.3%) were singletons, 290 (20.1%) were products of twin pregnancies and 9 (0.6%) infants were triplets. While the three sets of triplets were of non-IVF conceptions, 246 of the 290 (84.8%) neonates born of twin pregnancies were products of IVF pregnancies. Thus, out of 504 IVF neonates, 258 (51.2%) were singletons. There were 246 (48.8%) live births from 127 twin pregnancies (in 8 of the 127 twin pregnancies, there was intrauterine demise of one twin resulting in a total of 246 live-births instead of the expected 254). There were 243 (48.2%) females and 261 (51.8%) males in this cohort of IVF neonates.

*Senior Advisor (Paediatrics & Neonatology), INHS Kalyani, Vishakhapattanam. #Senior Advisor (Paediatrics & Paediatric Neurology),
+Senior Advisor (Paediatrics & Paediatric Cardiology), **Senior Advisor (Obstetrics, Gynaecology & ART), ##Senior Advisor (Obstetrics &
Gynaecology), ***Senior Advisor (Obstetrics & Gynaecology & Gynaecology Oncology), ++Classified Specialist (Obstetrics & Gynaecology),
Army Hospital (R & R), New Delhi-110 010.

Maternal ages ranged from 20 to 51 years with majority in the age group of 26 and 35 years (n=289; 74.1 %). Primary infertility was the underlying factor for 367 (72.8%) neonates and secondary infertility in 137 (27.2%).

The commonest maternal blood group was 'B positive' (124/385; 32.2%) followed by 'O positive' (118/385; 30.6 %). There were 102 (26.5%) 'A positive' group mothers while 'AB positive' group was the rarest (27/385; 7.1%). While 14 (3.6 %) mothers were Rh negative, none of them had Rh isoimmunisation. The commonest antenatal morbidity was pregnancy induced hypertension (PIH), seen in 75 (19.5%) mothers followed by hypothyroidism in 29 (7.5%) and gestational diabetes in 15 (3.9%). Overall, any maternal illness posing specific risk to the neonate was present in 165 out of 504 (32.7%) of all births.

More than half (283/504; 56.2%) of the neonates were delivered by lower segment caesarean section (LSCS), while 190 (37.7%) were delivered vaginally. The overall lower segment caesarean section rate was 54.02% (208/385 pregnancies) with LSCS being performed for 48.8% of singleton pregnancies (126/258) and for 64.6% (82/127) of twin pregnancies. Emergency LSCS was more common in singleton pregnancies (76/126; 60.03%) while elective LSCS was performed more frequently (55/82; 67.1%) in twin pregnancies.

There were 265 (52.6%) term and 239 (47.4%) preterms. Most (385; 76.4%) were appropriate for gestational age, 22.6% (n = 114) were small for gestational age while 5 (0.99%) neonates were large for gestational age.

The overall mean weight was 2408.36 ± 678.81 gms, the median weight 2500 gms with the minimum being 540 gms and the maximum 4100 gms. Low birth weight neonates (242/504) formed just under half the cohort (48.1%). The neonatal characteristics are depicted in Table 1.

A total of 62 (12.3%) neonates needed some form of resuscitation at birth. Of the 504 IVF neonates, 128 (25.4%) needed intensive care as compared to 187 (19.9%) out of 939 non-IVF neonates. Of the 315 inborn neonates who received intensive care during the study period, IVF neonates accounted for 128/315 (40.6 %) of all inborn admissions.

There were 474 (94.1%) survivors and of the 30 (5.9%) who died, six (20.0%) died within the first 24 hours, 21 (70.0%) within 7 days and the other three (10.0%) not surviving the neonatal period. Primary cause of death in terms of major system affected was as follows : respiratory in 15/30 (50.0%), infection in 6/30 (20%), cardiac anomaly in 1 (3.3%) and other systems in 8/30 (26.7%). The neonatal mortality rate (NMR) for the cohort of IVF neonates was 59.5 per 1000 live births.

Congenital anomalies were detected in 20 (3.9%) of the cohort (Table 2). A total of 29 (6.1%) neonates needed readmission within the neonatal period. All 29 survived the neonatal period (Table 3).

Discussion

Over the last two decades, IVF as a mode of conception for infertile couples has become an

Table 1

Neonatal characteristics of IVF conceptions (n=504)

Characteristic	Number of neonates	Percentage of total	Remarks
Gestation			
Term	265	52.6	Any infant < 37 weeks (completed) gestation taken as preterm
Preterm	239	47.4	
Weight for Gestation			
Appropriate	385	76.4	
Small	114	22.6	
Large	05	0.99	
Sex			
Females	243	48.2	
Males	261	51.8	
Weight categories			
< 1000 gm	018	03.6	
1000-1499 gm	031	06.2	
1500-2499 gm	203	38.3	
2500 gm or more	262	51.9	
Number			
Singletons	258	51.2	High twin incidence iatrogenic
Twins*	246	48.8	

*Number of neonates who are products of twin pregnancies is depicted here

established modality of intervention. It is estimated that world over, about 2,00,000 babies have been born with the use of Assisted Reproductive Technology (ART) by the year 2000 [6].

Majority (74.1%) of mothers in our study were in the age group of 26 to 35 years. It is expected that mothers undergoing IVF will be older than spontaneously conceiving mothers. Our cohort had younger mothers as compared to those reported by the Society for Assisted Reproductive Technology and American Society for Reproductive Medicine in 2002 where at least 50% of mothers were over 35 years of age [7]. This probably reflects early diagnosis of infertility and referral of couples needing ART in the Armed Forces which could have influenced our results positively.

The LSCS rate of 56.2% in this study is much higher than the 25.7% for double embryo transfers and 26.8% for single embryo transfers reported in a recent study of 499 IVF neonates [8]. Though it is well known that the threshold for intervention in IVF pregnancies is very low, this high LSCS rate needs further study.

In this study, there were 127 (32.98%) twin conceptions and 258 (67.02%) singleton pregnancies. This compares well with the reported rates of 24.3% twin pregnancies from the Danish National IVF Registry [9], 46% from Manchester [10], 23% from the Bourn-Hallam Group [11] and 44.5% from a large cohort of 31582 babies born in the years 1997-2000 after IVF [12]. Our study does not have any higher order births

Table 2**Congenital anomalies in IVF neonates (n=20)**

No of infants	Nature of anomaly	Mode of Diagnosis	Management	Remarks
1	Biliary hypoplasia with cirrhosis	Per-op cholangiogram	Underwent split liver transplantation	First twin; other twin normal
2	Capillary hemangioma	Visual	Local steroid infiltration (01)	Regression of lesion
1	Hirschsprung's disease	Contrast radiograph	Advised biopsy; refused	Died of acute colitis at 5 months 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 & karyotyping normal	On follow-up
2	Port wine stain face	Visual	Neuroimaging/ophthalmology normal	On follow-up
5	Minor anomalies	Polydactyly 01; Preauricular tags 01; Partial Iris atrophy 01; Labial fusion 01; Large head 01	On follow-up	On follow-up
2	Antenatal PUJ obstruction	USG; DTPA and GHA postnatally	Obstruction resolving	On follow-up
1	Prune Belly syndrome	Visual	Died soon after birth	Other twin normal
1	Hypospadias	Visual	On follow-up	On follow-up
1	Stridor	Large thymic mass on imaging	Mass surgically removed	On follow-up

Table 3**Readmissions during neonatal period in IVF neonates (n=29)**

No of infants	Nature of morbidity	Day of life readmitted	Management	Remarks
12	Neonatal hyperbilirubinemia	Days 3,4,5,6,7,8,9,14.	Phototherapy	All responded to phototherapy
6	Sepsis	Days 8,11,14,15,17	Antibiotics	One MSSA, others clinical sepsis
3	Feeding difficulties	Days 11,13,14	Supervised breast feeding	All improved
1	Aspiration Pneumonia	Day 25	Antibiotics and chest physiotherapy	Improved
1	Seizure disorder	Day 8	Phenobarbitone	Seizure free, off drugs and development normal at 7 months
1	Gastroesophageal reflux	Day 16	Domperidone for 1 month, off drugs now	Radionuclide milk scan diagnosis
1	Hirschsprung's disease	Day 6	Advised surgery	See 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

beyond twins. In our centre we limit the transferred embryos to two as transferring more embryos only increases the risk of multiple births and neonatal complications without significantly improving pregnancy rates [13].

This study had 47.4% premature neonates. IVF pregnancies are known to have higher rates of preterm deliveries [1] with different studies reporting rates of 23.8% [9], 34.9% [10], 25% [11] and 29.4% [14]. The higher rate of preterms in this study as compared to western studies may be due to the higher prematurity incidence even in non-IVF births in our country.

The percentage of low birth weight neonates is also

high in IVF babies with reported rates of 23.6% [9], 43.2% [10], 32% [11] and 20.5% [14]. Our low birth weight rate of 48.1% compares well with the range across various studies. Our study reports 22.6% 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 [15]. Another study has reported double incidence of small for gestational age in IVF neonates than in non-IVF neonates [8].

A fourth of all IVF neonates in this study needed intensive care. The increased morbidity and need for intensive care amongst IVF neonates is well known given

the high-risk group that they belong to [10,16]. Many studies report up to twofold increase in mortality rates for IVF neonates [1,8,11,12]. In our study the NMR was 59.4 per 1000, which is higher than the national NMR of 44/1000 but not twice the rate for non-IVF babies.

The rate of congenital anomalies in this cohort was 3.9% which is higher than the 2.5% reported in the Bourn Hallam group [11], but was lower than the 5.21% [8], 4.8% [9] and 6.1% [10] reported in other studies. 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 29 (6.1%) survivors needing re-admissions were mostly due to hyperbilirubinemia 12/29 (41.4%). 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. This is probably reflected by the low rate of readmission for feeding difficulties in our study. We are aware that there are additional risks of developmental delay [5], increased hospitalisations and illnesses during the first three years of life amongst IVF babies [1,16] as well as disorders due to abnormal imprinting [12] and therefore, follow-up of these infants is needed.

In conclusion, IVF neonates are at risk of multiple births, increased rates of prematurity and low birth weight as well as increased NMR, but the 94.1% survival rates in this study shows that there is hope for the infertile couples who long for parenthood.

Conflicts of Interest

None identified

Intellectual Contribution of Authors

Study Concept : Surg Capt S Narayan, Col KS Rana, Col K Kapur, Col M Sharma

Drafting & Manuscript Revision : Surg Capt S Narayan, Col BK Goyal, Lt Col P Talwar

Study Supervision : Col RK Sharma, Col M Sharma, Col KS Rana, Col K Kapur

References

- Koivurova S, Hartikainen AL, Sovio U, Gissler M, Hemminki E, Jarvelin MR. Growth, psychomotor development and morbidity up to three years of age in children born after IVF. *Hum Reprod* 2003; 18: 2328-36.
- Hansen M, Bower C, Milne E, Klerk N, Kurinczuk JJ. Assisted reproductive technologies and the risk of birth defects: A systematic review. *Hum Reprod* 2005; 20: 328-38.
- Anthony S, Buitendijk SE, Dorrepaal CA, Lindner K, Braat DDM, den Ouden AL. Congenital malformations in 4224 children conceived after IVF. *Hum Reprod* 2002; 17: 2089-95.
- Ercison A, Kallen B. Congenital malformations in infants born after IVF: a population-based study. *Hum Reprod* 2001; 16: 504-9.
- Stromberg B, Dahlquist G, Ericson A, Finnstrom O, Koster M, Stjernqvist K. Neurological sequelae in children born after in-vitro fertilisation: a population-based study. *Lancet* 2002; 359: 461-5.
- Adamson GD, Mouzon J, Lancaster P, Nygren KG, Sullivan E, Zegers-Hochschild F. World collaborative report on in vitro fertilisation, 2000. *Fertil Steril* 2006; 85: 1586-622.
- Society for Assisted reproductive Technology and American Society for Reproductive Medicine (2002). Assisted Reproductive Technology in the United States: 1998 results generated from American Society for Reproductive Medicine/ Society for Assisted Reproductive Technology Registry. *Fertil Steril* 2002; 77: 18-31.
- Poikkeus P, Gissler M, Unkila-Kallio L, Hyden-Granskog C, Tiitinen A. Obstetric and neonatal outcome after single embryo transfer. *Hum Reprod* 2007; 22: 1073-9.
- Westergaard HB, Tranberg-Johansen AM, Erb K, Anderson AN. Danish National In-Vitro Fertilisation Registry 1994 and 1995: A controlled study of births, malformations and cytogenetic findings. *Hum Reprod* 1999; 14: 1896-902.
- D'Souza SW, Rivlin E, Cadman J, Richards B, Buck P, Lieberman BA. Children conceived by in vitro fertilisation after fresh embryo transfer. *Arch Dis Child Fetal Neonatal Ed* 1997; 76: 70-4.
- Rizk B, Doyle P, Tan SL, Rainsbury P, Betts J, Brinsden P, et al. Perinatal outcome and congenital malformations in in-vitro fertilisation babies from the Bourn-Hallam group. *Hum Reprod* 1991; 6: 1259-64.
- Reynolds MA, Schieve LA, Martin JA, Jeng G, Macaluso M. Trends in multiple births conceived using assisted reproductive technology, United States, 1997-2000. *Paediatrics* 2003; 111: 1159-62.
- Templeton A, Morris JK. Reducing the risk of multiple births by transfer of two embryos after in-vitro fertilisation. *N Engl J Med* 1998; 339: 573-7.
- Reefhuis J, Honein MA, Schieve LA, Correa A, Hobbs CA, Rasmussen SA. The National Birth Defects Prevention Study. *Hum Reprod* 2009; 24: 360- 6.
- Koudstaal J, Braat DDM, Bruinse HW, Naaktgeboren N, Vermeiden JPW, Visser GHA. Obstetric outcome of singleton pregnancies after IVF: a matched control study in four Dutch university hospitals. *Hum Reprod* 2000; 15: 1819-25.
- Hansen M, Colvin L, Petterson B, Kruinczuk JJ, de Klerk N, Bower C. Admission to hospital of singleton children following assisted reproductive technology (ART). *Hum Reprod* 2008; 23: 1297-305.