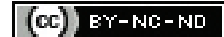


Morbidity and Mortality Patterns of Neonates Born to Multiple Pregnancies: A Prospective Observational Study

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ABSTRACT

Introduction: In the last few decades, the prevalence of multiple pregnancies has increased, and it is associated with significantly higher maternal and neonatal mortality.

Aim: To determine the morbidity and mortality patterns of neonates born to multiple pregnancies.

Materials and Methods: Prospective observational study was undertaken on neonates who were born to a mother with multiple gestations. One hundred mother's neonates with multiple pregnancies were consequently enrolled at a tertiary institute for six months. Morbidity and mortality patterns were analysed. The data regarding the numerical variables were summarised through percentage, average, median, and deviation patterns and comparisons of categorical data were carried out by using Pearson's Chi-square test.

Results: A total of 202 babies was delivered including two pairs of triplets. Among that two were still born and two were Intra Uterine Deaths (IUD). Most of the twin pregnancies were spontaneous and in the maternal age group of 21-25 years.

The male to female ratio was almost equal and 148 (74.75 %) neonates were preterm. One hundred and seventeen (59.09%) neonates were Low Birth Weight (LBW) and 44 (22.22%) were Very Low Birth Weight (VLBW), including 85 (42.93%) Small for Gestational Age (SGA) and 43 (21.72%) were Intrauterine Growth Retardation (IUGR). Ninety-eight (49.49%) neonates' required Neonatal Intensive Care Unit (NICU) admission with lethargy and respiratory distress being the common clinical presentation. Respiratory distress syndrome, sepsis and birth asphyxia was diagnosed in 44.9%, 24.5% and 5.1% neonates respectively while jaundice, intraventricular haemorrhage and retinopathy of prematurity were the clinical diagnosis. Perinatal mortality rate was 163.34 per 1,000 pregnancies while the neonatal mortality rate was 146.46 per 1000 live born neonates. Respiratory distress syndrome, sepsis and the intraventricular haemorrhage were the common causes of mortality.

Conclusion: Prevention of prematurity and LBW neonates is the key to reduce mortality and it is the greatest challenge to paediatricians and obstetricians.

Keywords: Neonatal morbidity and mortality, Perinatal mortality, Twin neonates, Twin pregnancy

INTRODUCTION

In the past three decades, the prevalence of multiple pregnancies has increased particularly in high and middle income countries due to an increase in the use of assisted reproductive technologies, advancing maternal age, and a decline in fertility [1]. The rate of natural twin pregnancy varies from 6-9 per 1,000 pregnancies in East Asia/Latin America, 8-16 in Europe, North America, the Middle East, and they are as high as 18 or more in Central Africa; and the highest rate recorded is in Nigeria and lowest in Japan [2-4]. In India, twin pregnancy rate varies from 3-7 per 1,000 deliveries [5,6]. Incidence of monozygotic twins is uniform all over the world but dizygotic twin pregnancies varies and is significantly associated with race, genetic, maternal age, parity and the use of assisted reproductive techniques [7].

Although multiple births are associated with significantly higher maternal and neonatal morbidity and mortality, being successfully blessed with more than one baby in a single pregnancy, allows a family to expand instantaneously at the same time reducing the number of labour experiences for them. Multiple births are associated with a four-fold increase in fetal death and six fold increases in neonatal death and it is believed that gestational age and birth weight differences are the most important independent predictors of mortality [8].

According to literature, neonatal mortality and morbidity including preterm birth, LBW, respiratory distress, discordance between weights of twins and twin to twin transfusion syndrome significantly increased in multiple pregnancies compared to single ones. Twin pregnancies are also associated with a

13 fold and five fold increase in still births in monochorionic and dichorionic twins compared to singleton pregnancies [9-12]. In India, most of the published data, on multiple births are reported by obstetricians and a very few emphasis was given about neonatal outcomes [5,6,13,14]. So, this study was conducted to know the neonatal morbidity and mortality patterns in neonates born to multiple pregnancies.

MATERIALS AND METHODS

This prospective observational study was undertaken on neonates who were born to mother with multiple gestations after approval from the Institutional Ethical Committee (No 2043/EC/Pharmac/GMC/NGP/Dated 04/05/2020) and informed valid consent from parents at one of the largest tertiary care teaching government referral hospital that provide care to underprivileged, socioeconomically deprived population of central India. The study duration was six months (from March 2020 to August 2020). Our hospital is a 1200 bedded tertiary health care facility and attached to it is a 400 bedded super speciality hospital. Monthly around 1200-1500 pregnant mothers deliver and around 10-15 neonates were admitted in NICU. The NICU is equipped with radiant warmer, phototherapy units, central oxygen supply, bubble Continuous Positive Airway Pressure (CPAP), neonatal ventilators and facilities for dialysis and surfactant therapy.

Inclusion criteria: Neonates of either sex, irrespective of their gestational age and birth weight born to mothers with multiple gestations.

Exclusion criteria: Neonates whose parents left the hospital against medical advice and were not willing to participate in the study.

Sample size was calculated with considering of expected proportion of 15%, absolute precision of 20% and confidence interval of 95%, and calculated according to following formula:

$$N = Z_{1-\alpha}^2 \times p(1-p)/d^2$$

where, α =Level of significance; $Z_{1-\alpha}$ =Corresponding normal standard variant; p =Expected proportion; d =Absolute precision and $n=85$. But, the present study recorded data of 100 mothers with multiple pregnancies.

Data were collected following admission, from either the mother or the caregiver in a structured data sheet. Maternal details including age, gravida/parity status, details of antenatal care, obstetrics complications, and mode of delivery were recorded. All the neonates were attended by residents posted in neonatology and Apgar score was documented. Neonatal data included gestational age (assessed by either menstrual history of mother, available ultrasound report or by New Ballard Scoring) [15], gender, birth weight/weight on admission, clinical presentation and duration of hospital stay. Healthy neonates were observed in the maternity ward, and shifted in NICU, if

any complications were noted. All neonates were investigated, managed and monitored as per the standard treatment protocol till discharge or death. Diagnosis of neonatal illness and estimation of the cause of death was done using clinical information and necessary laboratory investigation.

The following working definition were used in this study-[16,17].

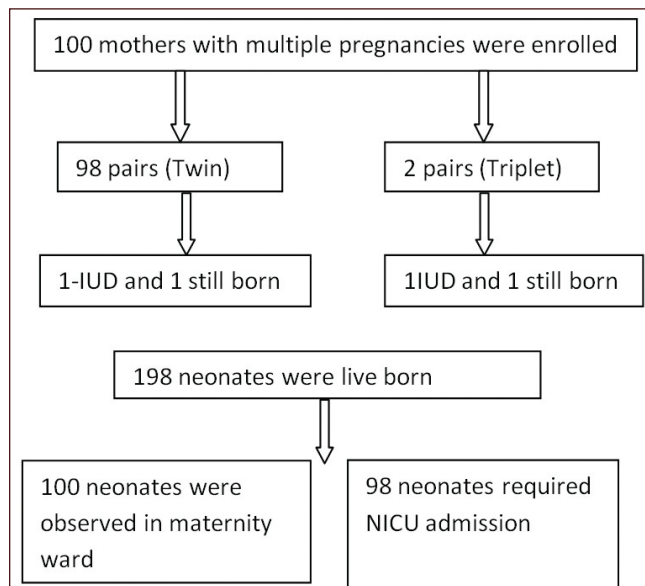
- Hypothermia (axillary temperature by digital thermometer), capillary refill time (>3s was taken as prolonged), blood sugar (<40 mg/dL was taken as hypoglycaemia) and other life threatening events were recorded.
- Birth asphyxia was considered in the presence of failure to establish breathing at birth.
- Respiratory distress was diagnosed in the presence of at least two of the following criteria: (1) respiratory rate >60/min recorded for at least one minute; (2) chest in drawing; and (3) expiratory grunt/roaring.
- Meconium Aspiration Syndrome (MAS) was diagnosed in the presence of two of the following: 1) meconium staining of liquor or staining of nails or umbilical cord or skin; (2) respiratory distress soon after birth/within 1 hour of birth; and (3) radiological evidence of aspiration pneumonia (atelectasis and/or hyperinflation)
- Clinical sepsis was defined as neonate having symptoms and/or sign of sepsis with maternal risk factors of infection. Probable sepsis was clinical sepsis with a positive septic screen and confirmed sepsis was defined as that with the growth of the causative organism in blood culture. Early Onset Sepsis (EOS) was defined as clinical manifestation of sepsis appearing within 72 hours of birth, while in Late Onset Sepsis (LOS), clinical manifestation of sepsis appeared after 72 hours of birth.
- Small for Gestational Age (SGA): Weight below the 10th percentile for the gestational age.
- Low Birth Weight (LBW): Birth weight of less than 2500 gm
- Very Low Birth Weight (VLBW): Birth weight of less than 1500 gm
- Extremely Low Birth Weight (ELBW): Birth weight of less than 1000 gm

STATISTICAL ANALYSIS

The data were entered into Microsoft excel sheet and analysis was done using software STATA version 14 (Texas USA). The data regarding the numerical variables were summarised through percentage, average, median, and deviation patterns. Comparisons of categorical data were carried out by using Pearson's Chi-square test. The p-value <0.05 was taken as statistically significant.

RESULTS

A total of 202 babies were delivered by 100 mothers including two pairs of triplets. Among 202 babies, two were still born and two were IUD; as a result, 198 were live born [Table/Fig-1].



[Table/Fig-1]: Flow chart of study population.

NICU: Neonatal intensive care unit; IUD: Intrauterine deaths

Fifty eight percent (58%) mothers were falling into age the group of 21-25 years and most of the mothers were from rural area. History of infertility was recorded in 14 mothers and they had received ovulation inducing agents. Previous abortion was noted in 22 mothers while previous intrauterine death and still born were observed in two mothers each [Table/Fig-2].

Among 198 live born neonates, 102 (51.52%) were male and the male to female ratio was 1.06:1. Amongst twin neonates; 25 pairs were both female, 27 pairs were both male and 46 pairs were of different sex while two pairs of triplet of one female and two male in each pair. One hundred and seventeen neonates were LBW (59.09%) while 44 (22.22%) were VLBW. One hundred and twelve (56.57%) neonates were born by caesarean delivery. Resuscitation was required in 18 (9.09%) neonates and 98 (49.49%) neonates required NICU admission [Table/Fig-3].

Lethargy, respiratory distress and jaundice were the clinical presentation in 59 (60.20%), 44 (44.90%) and 20 (20.41%) respectively while cyanosis was noted in 8 (8.16%) neonates. Respiratory distress ($p < 0.001$), low oxygen saturation ($p = 0.003$), mean low temperature ($p = 0.004$) and low mean serum calcium level ($p < 0.0001$) were significantly associated with higher mortality. Lethargy was the most common clinical presentation and it was the most favorable clinical feature for survival [Table/Fig-4].

Respiratory distress syndrome was diagnosed in 44 (44.90%) neonates mainly in extreme and early preterm neonates.

| Characteristics | Total mothers n=100 (%) |
|---|-------------------------|
| Maternal age (Years) | |
| 18-20 | 1 (1) |
| 21-25 | 58 (58) |
| 26-30 | 31 (31) |
| ≥31 | 10 (10) |
| Duration since marriage (Years) | |
| 1-<5 | 68 (68) |
| 5-10 | 27 (27) |
| >10 | 5 (5) |
| Residence | |
| Rural | 65 (65) |
| Urban | 35 (35) |
| Gravida | |
| Primigravida | 49 (49) |
| Multigravida | 51 (51) |
| History of Infertility (Yes) | |
| | 14 |
| Primary infertility | 9 (64.29) |
| Secondary infertility | 5 (35.71) |
| Use of ovulation inducing agent | 14 (14) |
| H/o previous abortion | 22 (22) |
| H/o previous still birth | 2 (2) |
| H/o previous intra uterine death | 2 (2) |
| H/o previous multiple births | 10 (10) |
| Maternal Illness | |
| Anaemia | 57 (57) |
| Hypertension | 14 (14) |
| Hypothyroidism | 9 (9) |
| Hyperthyroidism | 1 (1) |
| Psychiatric disorder | 2 (2) |
| Kidney diseases | 5 (5) |
| Diabetes | 7 (7) |
| Genital Tuberculosis | 3 (3) |
| Hepatitis | 2 (2) |
| Obstetric complication | |
| Gestational diabetes | 3 (3) |
| Pre-eclampsia | 25 (25) |
| Eclampsia | 7 (7) |
| Antepartum haemorrhage | 2 (2) |
| No obstetrics complications | 63 (63) |
| [Table/Fig-2]: Maternal characteristics of study population. | |
| H/o- History of | |

Intraventricular haemorrhage was evident in 6 (6.12%) extreme and early preterm neonates and retinopathy of prematurity in 5 (5.1%) early and moderate preterm neonates who required

| Characteristics | Total mothers (n=100, %) |
|-------------------------------------|--------------------------|
| Gender | |
| Male | 102 (51.52) |
| Female | 96 (48.48) |
| Gestational age | |
| Extreme preterm (<28 weeks) | 10 (5.05) |
| Early preterm (29-31 weeks) | 26 (13.13) |
| Moderate preterm (32-33 weeks) | 34 (17.17) |
| Late preterm (34-36 weeks) | 78 (39.4) |
| Term (37-42 weeks) | 50 (25.25) |
| Birth weight (gm) | |
| ≤1000 | 12 (6.06) |
| 1001-1499 | 44 (22.22) |
| 1500-2499 | 117 (59.09) |
| 2500-2999 | 25 (12.63) |
| Mode of delivery | |
| Vaginal | 86 (43.43) |
| Cesarean | 112 (56.57) |
| Cried immediately after birth (Yes) | 180 (90.91) |
| Resuscitation required (Yes) | 18 (9.09) |
| Apgar score (mean±SD) | |
| At 1 minute | 7.76±0.95 |
| At 5 minute | 8.81±0.74 |
| At 10 minute | 8.56±1.69 |
| Average for gestational Age | 70 (35.35) |
| Small for gestational Age | 85 (42.93) |
| Intra uterine growth restriction | 43 (21.72) |
| NICU admission required | 98 (49.49) |
| Observation in maternity ward | 100 (50.51) |

[Table/Fig-3]: Neonatal characteristics of study population.
NICU: Neonatal intensive care unit; SD: Standard deviation

prolonged oxygenation. Sepsis was evident in 24 (24.5%) neonates among which 15 (62.5%) had early onset while 9 (37.5%) had LOS. Clinical, probable and proven sepsis was diagnosed in 11 (45.83%), 8 (33.33%) and 5 (20.83%) neonates respectively. Most common isolated organism was E. coli in three neonates followed by Klebsiella and Acinetobacter one in each. Birth asphyxia was diagnosed in 5 (5.1%) neonates and most of them were term neonates born to elderly mothers. Hypoxic-ischemic encephalopathy (HIE) stage I was diagnosed in three neonates and each one neonates had HIE II and HIE III [Table/Fig-5] [16,17].

Perinatal mortality rate was 163.34 per 1000 pregnancies (including two still born and two intrauterine deaths) while neonatal mortality rate was (29/198) 146.46 per 1000 live births. Average duration of hospital stay for non-survivors was

shorter (6.1±2.81 days) compared to survivors (12.6±4.50 days) neonates. Mean age of mother among dead neonates was 24.33 years (range 22-40 years) and most of the twin pregnancy

| Clinical/Laboratory variables | Total admission (n=98) | Survival (n=69) | Non survival (n=29) | p-value |
|---------------------------------|------------------------|-----------------|---------------------|---------|
| Lethargy | 59 (60.20) | 56 (81.16) | 3 (10.34) | <0.001 |
| Hypothermia | 4 (4.08) | 4 (5.8) | 0 | 0.44 |
| Respiratory distress | 44 (44.90) | 22 (31.88) | 22 (75.86) | <0.001 |
| Jaundice | 20 (20.41) | 15 (21.74) | 5 (17.24) | 0.8 |
| Cyanosis | 8 (8.16) | 6 (8.7) | 2 (6.9) | 1 |
| Prolonged capillary refill time | 2 (2.04) | <0.001 | 2 (6.9) | 0.15 |
| Oxygen saturation (%) | 94.5±0.70 | 93.4±0.60 | 87.8±15.58 | 0.003 |
| Temperature on arrival (°C) | 36.08±0.19 | 36.1±0.22 | 35.94±0.30 | 0.004 |
| Blood sugar (mg%) (mean±SD) | 76±6.65 | 75.4±8.82 | 76.71±12.92 | 0.5 |
| Serum Calcium (mg%) (mean±SD) | 9.0±0.23 | 9.2±0.55 | 8.7±0.45 | <0.0001 |
| Leucocytes (mean±SD) | 9200±1979.89 | 9800±2023.92 | 10600±2151.74 | 0.08 |
| C-reactive protein (Positive) | 10 (10.20) | 6 (8.7) | 4 (13.79) | 0.47 |

[Table/Fig-4]: Clinical variables (not exclusive) on NICU arrival (Chi-square test).

SD: Standard deviation; p value<0.05 was taken as statistically significant

| Clinical diagnosis | All cases (n=98, %) | Mortality (n=29, %) |
|-------------------------------|---------------------|---------------------|
| Sepsis | 24 (24.50) | 6 (20.7) |
| Respiratory distress syndrome | 44 (44.90) | 15 (51.72) |
| Birth asphyxia | 5 (5.1) | 1 (3.44) |
| Meconium aspiration syndrome | 3 (3.06) | 2 (6.9) |
| Jaundice (not exclusive) | 11 (11.22) | 5 (17.24) |
| Intraventricular haemorrhage | 6 (6.12) | 5 (17.24) |
| Retinopathy of prematurity | 5 (5.1) | 0 |

[Table/Fig-5]: Morbidity and mortality pattern of neonates.

was spontaneous, only four mothers had history of primary infertility and they received ovulation inducing agent. Twenty-two (75.86%) non survival were delivered by vaginal route. All non survival neonates were preterm except one who died because of severe birth asphyxia. Ten pair of twins and one pair of triplet succumbed. Five pair of twins had same sex with gestational age range from 27-31 weeks and birth weight range from 600 gm to 1400 gm. Most common cause of death was respiratory distress

syndrome in 15 (51.72%), followed by sepsis 6 (20.7%) and intra-ventricular haemorrhage in 5 (17.24%). One term neonate with birth asphyxia and two late preterm neonates with MAS were expired. Surfactant therapy and inotropic support was needed in seven and six neonates respectively, among them five neonates expired with each therapy. Bubble CPAP was given in 33 neonates and 18 died while ventilators CPAP therapy was received by eight neonates out of which seven expired. Invasive ventilation therapy was provided for seven neonates and six neonates succumbed out of those.

DISCUSSION

In present study, 58% mothers were in the age group between 21-25 years. The present findings are in agreement with most of the Indian authors because in India, marriage and conception occurs at an early age while literature from other countries revealed higher age of mothers [3,4,13,18]. In current study, most of the mothers were from rural area as the institute is one of the largest referral centre in central India. Similar to the finding reported by Pandey MR et al., (51% multigravida mothers), the present study observed 49% primigravida and 51% multigravida mothers but Singh L and Trivedi K, (70.67%) and Tasnim S et al., (78.5%) reported higher number of multigravida mothers in their study [18-20]. It is a well-known fact that ovulation inducing agent and assisted reproductive technologies are widely used in infertile mother and this advancement in medical field lead to the increased number of multiple pregnancies [11,12]. The factors responsible for twinning like genetics (10 mothers had previous twin pregnancies) and infertility treatment (14 mothers had ovulation induction done) were significantly reported in present study also.

In present study, 198 neonates were live born and male to female ratio was 1.06:1. Such a male predominance was reported by Tasnim S et al., and Monden CWS and Smits J, but female outnumbered males in a study done by Sabzehei MK et al., from Iran and also in a Nigerian study [2,3,20,21]. The present study observed, 46/98 (46.94%) pairs of different sex neonates while, 52/98 were of the same sex with 27 pairs of male neonates (27.55%) and 25 pairs of female neonates (25.51%). Out of the two pairs of triplets, each pair simultaneously had one female and two male neonates, and present findings were concomitant with Arora GG et al., [6]. SGA and IUGR are common in multiple pregnancies due to the compromised space for growth, demand of excess nutrition and obstetric complication. The present study found 42.93% and 21.72% neonates were SGA and IUGR respectively. Though, neonatal morbidity was lower in vaginally delivered neonates but neonatal death is not associated with the mode of delivery. Still the rate of cesarean section is on the rise worldwide especially for the second neonates due to malpresentation, and the present study observed 56.57% neonates were born by cesarean section [10,22].

In the present study, 98 (49.49%) neonates required admission in NICU. Clinical presentation like respiratory distress ($p < 0.001$), low oxygen saturation ($p = 0.003$), low temperature ($p = 0.004$) at arrival and low serum calcium ($p < 0.0001$) were significantly co-related with mortality. This might be because of lower gestational age and smaller weights on admission who were more fragile and were more prone for mortality. Other researchers also reported that twin neonates more frequently needed NICU admission compared to singletons neonates [14,19,21]. It has been shown that prematurity and LBW is significantly higher in twin pregnancy. The present study observed, 87.37% of LBW neonates, consistent with observations noted in other studies like Arora GG et al (93.01%) and Tasnim S et al., (80%), while 74.5% of premature neonates which were significantly higher than other studies (Arora GG et al., 3.91% and Tasnim S et al., 27.2%). Similar to the observation of other researchers SGA and intrauterine growth retarded neonates are higher (42.93% and 21.72%) compared to average for gestational age (35.35%) [3,7,19].

A study done by Sabzehei MK et al., reported a significantly higher number of twin neonates had respiratory distress syndrome, hypoglycaemia and requirement of phototherapy and Singh L and Trivedi K, observed higher incidence of moderate to severe birth asphyxia in twin neonates compared to singletons neonates [19,21]. In the present study, 44.9%, 6.12%, and 5.1% neonates had respiratory distress syndrome, intraventricular haemorrhage and retinopathy of prematurity respectively. Respiratory distress syndrome was more common because around two-third of the neonates were preterm similar to Basiri B et al., work which reported respiratory distress syndrome in 82% neonates. Sepsis was evident in 24.50% neonates as opposed to 14% reported by Basiri B et al., [22]. Microorganism was isolated in five of present study neonates and E-coli was the most common organism. Perinatal mortality rate in the present study was 163.34 per 1000 pregnancies while neonatal mortality rate was 146.46 per 1000 live births which are similar to the other researcher [22] Yadav CM et al., reported prematurity; birth asphyxia and sepsis as the common causes of perinatal deaths in twin neonates while present study reported respiratory distress syndrome, sepsis and intraventricular haemorrhage to be the most common causes in descending trend [23]. Similar to other authors, most of the sick neonates who required inotropic support, mechanical ventilation and surfactant therapy died. Prospectively done and monitored by paediatrician is the strength of the present study. This study recommends that reduction of preterm birth by effective antenatal care and timely intervention of acute life threatening events by paediatrician is very important to reduce the perinatal mortality.

Limitation(s)

Small sample size and short duration without follow-up.

CONCLUSION(S)

Most of the twin pregnancies were spontaneous and in the maternal age group of 21-25 years. About 49.49% neonates required NICU admission with lethargy and respiratory distress being the common presentation. Perinatal mortality rate was 163.34 per 1000 pregnancies while neonatal mortality rate was 146.46 per 1000 live born neonates. Respiratory distress syndrome and sepsis was the common cause of admission and deaths.

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PLAGIARISM CHECKING METHODS: ^[Jain H et al.] ETYMOLOGY: Author Origin

- Plagiarism X-checker: Sep 19, 2020
- Manual Googling: Jan 15, 2021
- iThenticate Software: Mar 04, 2021 (13%)

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Sep 18, 2020**
Date of Peer Review: **Dec 10, 2020**
Date of Acceptance: **Jan 21, 2021**
Date of Publishing: **Mar 31, 2021**