American Journal of Pediatrics
2024, Vol. 10, No. 4, pp. 220-228
https://doi.org/10.11648/j.ajp.20241004.20

Case Report

Management of Quadruplet Infants at the General Hospital of West Nusa Tenggara Province, Indonesia: A Case Report

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Abstract

Multiple pregnancies with more than two fetuses significantly increase maternal and infant complications. Almost all multiple pregnancies with more than two fetuses result in preterm birth. Prematurity is the main consequence of multiple pregnancies with more than two fetuses. Early provision of optimal nutrition is crucial for the growth and immunity of premature infants. We report our first-hand experience as the primary referral hospital in West Nusa Tenggara Province, Indonesia, in providing multidisciplinary care for the birth of quadruplet premature infants. A 39-year-old woman, gravida 3, para 2, living 2, nulliparous, was referred to the General Hospital of West Nusa Tenggara Province from Bima District Hospital due to a quadruplet pregnancy at 28-29 weeks gestation. A multidisciplinary team consisting of obstetricians, pediatricians, and nurses was assembled. All four infants were diagnosed with hyaline membrane disease (HMD) and immediately transferred to the Neonatal Intensive Care Unit (NICU). Premature infants received parenteral and enteral nutrition support. Family-centered care approach was implemented for the care of the premature infants and their families. All infants were discharged at 35 weeks postmenstrual age (PMA). Spontaneous quadruplet pregnancies are rare cases, and this particular case represents the first experience of our hospital in managing quadruplet infants. A well-coordinated multidisciplinary approach, coupled with good preparedness for delivery, is essential and has proven to yield favorable outcomes for both the mother and the infants.

Keywords

Quadruplet Pregnancy, Quadriplet, Premature Infant Management

1. Introduction

Multiple pregnancies involving more than two fetuses are the term used when more than two fetuses develop simultaneously in the uterus. This occurrence is rare, with an incidence ranging from 0.01% to 0.07% and categorized as a high-risk pregnancy [1]. The advancements in fertility medications and assisted reproductive techniques have increased the occurrence of multiple pregnancies, especially in older women [2]. Spontaneous multiple pregnancies, particularly quadruplet pregnancies, are extremely rare, with an incidence ranging from one in 512,000 to one in 677,000 births [3]. Multiple pregnancies with more than two fetuses significantly increase maternal and infant complications [2].

Twin infants have a fourfold higher risk of fetal death during pregnancy compared to singletons, a sevenfold higher risk of immediate postnatal death, a tenfold higher risk of neonatal intensive care unit (NICU) admission, and a sixfold higher likelihood of experiencing cerebral palsy [4]. The risks are even higher in triplet and quadruplet pregnancies. Addi-

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Received: 16 November 2024; **Accepted:** 29 November 2024; **Published:** 16 December 2024

tionally, multiple pregnancies pose risks to the mother, including intrauterine growth restriction, gestational diabetes, pregnancy-induced hypertension, miscarriage, anemia, preeclampsia, postpartum hemorrhage, and low birth weight, ultimately leading to increased neonatal morbidity and mortality [4].

Almost all multiple pregnancies with more than two fetuses result in preterm birth. Preterm birth increases morbidity and mortality in infants due to perinatal conditions or exposure to the external environment when the baby's organs are not fully developed [2]. Preterm birth accounts for approximately 27% of neonatal deaths worldwide and causes one million deaths annually, making it a leading direct cause of neonatal mortality [5]. Preterm birth of multiple infants substantially contributes to the overall rate of preterm births.

The management and care of neonates from pregnancies with more than two fetuses need to be conducted meticulously to reduce mortality and morbidity. Optimal nutrition through early initiation of adequate parenteral and enteral nutrition, along with family-centered care, plays a crucial role in promoting the growth and immunity of premature infants. Poor nutrition is associated with poor head circumference growth, which is linked to impaired psychomotor skills, cognitive abilities, cerebral palsy, and autism [6]. We report our first-hand experience as the primary referral hospital in West Nusa Tenggara Province, Indonesia, in providing multidisciplinary care for the premature birth of quadruplet infants.

2. Case Description

A 39-year-old woman with a G3P2L2D0 status was referred to the Regional General Hospital of West Nusa Tenggara Province from the District General Hospital of Bima due to a quadruplet pregnancy at 28-29 weeks of gestation. During the pregnancy, the patient reported having received treatment from a general practitioner and taking iron supplements. The patient had not received tetanus immunization during the course of the pregnancy. The first ultrasound at 4 months of gestation indicated a twin pregnancy, and the second ultrasound at 5-6 months of gestation still confirmed a twin pregnancy. However, at 7 months of gestation, the ultrasound revealed a quadruplet pregnancy, leading to an immediate referral for further management.

There were no reported medical history or complications during the pregnancy. The patient only complained of lower back pain and had no other complaints such as fever, cough, or shortness of breath. Previously, the patient had received corticosteroid injections for fetal lung maturation at the District General Hospital of Bima. In our hospital, a 6 mg dose of dexamethasone was administered to expedite fetal lung maturation. The patient was scheduled for an elective cesarean section due to the high-risk nature of the pregnancy. During the labor preparation at our hospital, the patient received nifedipine as a tocolytic, intravenous multivitamins, and lactated Ringer's solution. Physical examination revealed an overdistended abdomen with palpable fetal parts. There was no amniotic fluid leakage during the labor preparation. Hematological examination results showed a leukocyte count of 10,180/μL with 79.6% neutrophils and a hemoglobin level of 11 g/dL.

A resuscitation team was prepared prior to the cesarean section and consisted of obstetrician-gynecologists, pediatricians, and nurses (Figure 1). Four teams were assembled for neonatal resuscitation, equipped with four warmers/resuscitation beds, T-resuscitators, and four sets of resuscitation equipment. The elective cesarean section was successfully performed, resulting in the delivery of four male infants with a one-minute time interval between each birth. with 1 placenta and 4 amniotic sacs (monochorionic tetraamniotic).

Figure 1. *The prepared resuscitation team in managing quadruplet infants at the Regional General Hospital of West Nusa Tenggara Province (NTB) engaging in prayer before proceeding with the cesarean section procedure.*

The data for the four infants at the time of birth are provided in Table 1. Neonatal resuscitation was performed using the prepared infant warmers.

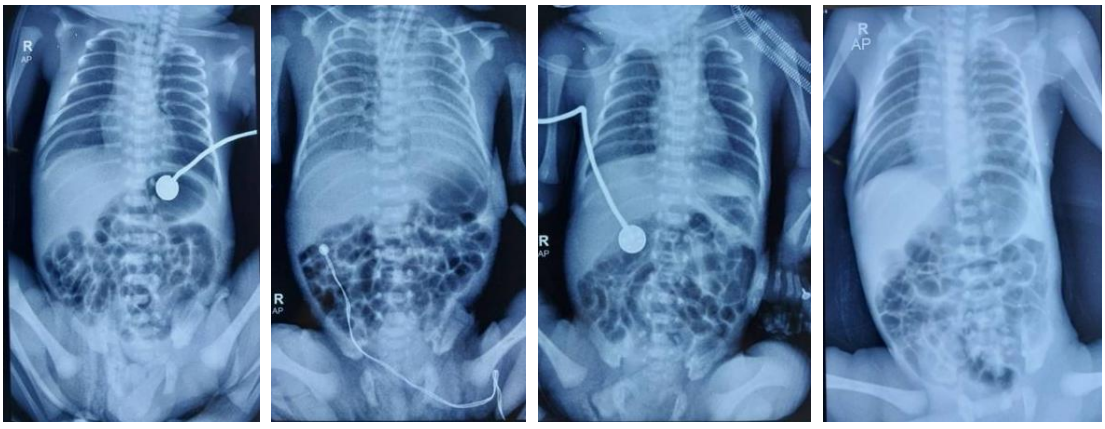
Table 1. *Details of the four infants at the time of birth.*

Quadruplet	G	BW	BL	HC	MUAC	APGAR	TOB
First	Male	1350	39	27	6,5	5-7	08.30
Second	Male	1370	40	27	6,5	3-5	08.31
Third	Male	1100	37	26	6	5-7	08.32
fourth	Male	1195	37	28	6	5-7	08.33

G: Gender
MUAC: Mid Upper Arm Circumference (cm)
BW: Body Weight (gram)
APGAR: APGAR scores at 1', 5'
BL: Body Length (cm)
TOB: Time of birth
HC: Head Circumference (cm)

Figure 2. *Pediatric specialist and team during the neonatal resuscitation process for the fourth infants.*

The first, third, and fourth infants were transferred to the Neonatal Intensive Care Unit (NICU) and placed on non-invasive ventilation, specifically Nasal Intermittent Positive Pressure Ventilation (NIPPV). The second infant was transferred to the NICU and placed on invasive ventilation, utilizing High-Frequency Oscillatory Ventilation (HFOV) as a supportive therapy (Figure 2). Each infant was ensured to have stable vital signs using a sensor monitor, IV line access was established, and antibiotics, aminophylline, and Total Parenteral Nutrition (TPN) were administered.

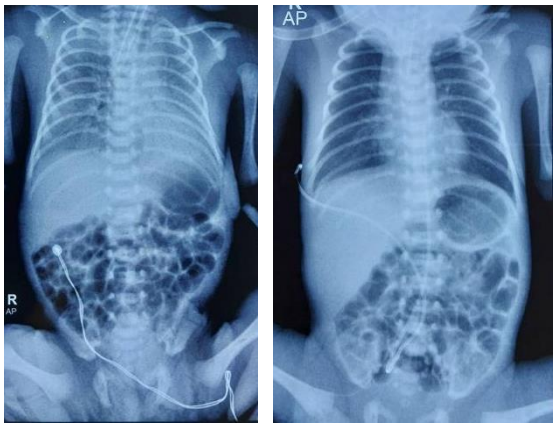


First baby Second Baby Third Baby Fourth baby

Figure 3. *Thoraco-abdominal X-ray image of the quadruplet babies showing features of Hyaline Membrane Disease (HMD).*

On the first day of treatment, the first baby was placed on NIPPV (Nasal Intermittent Positive Pressure Ventilation) with settings of 20/7, FiO2 23%, and maintained SpO2 levels between 95% and 96%. The second baby was intubated with endotracheal tube (ETT) size 3 and connected to the ventilator in HFO (High-Frequency Oscillation) mode, with settings of MAP 12,

Amplitude 25, FiO2 25%, and maintained SpO2 levels between 94% and 96%. The third baby was initially placed on NIPPV with settings of 20/6 and FiO2 25%, but experienced repeated desaturation. Subsequently, periodic suctioning was performed, and the baby was placed on NIPPV with settings of 21%-25% and PEEP 6. The fourth baby was also placed on NIPPV and showed improvement in ventilation on the first day of treatment. Blood gas analysis and thoraco-abdominal X-ray were performed for all babies. All thoraco-abdominal X-rays showed signs of Hyaline Membrane Disease (HMD), with the second baby exhibiting signs of Grade III HMD (Figure 2).



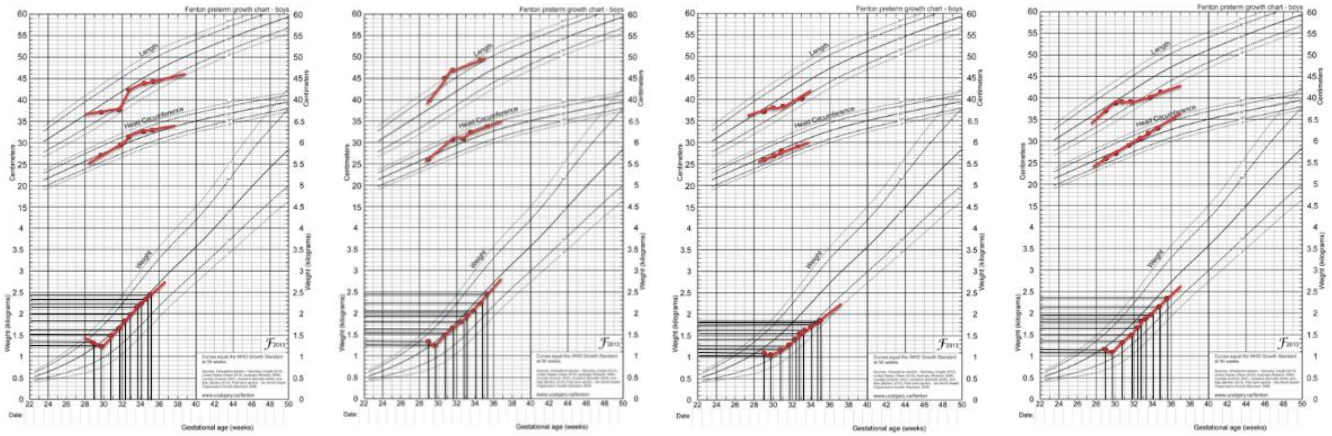
A B

Figure 4. *A. Thoraco-abdominal X-ray of the second baby shows inadequate lung expansion due to grade III HMD. B. Thoraco-abdominal X-ray of the second baby after surfactant therapy demonstrates improved lung expansion in both lung lobes.*

The second baby showed signs of clinical deterioration due to HMD, prompting us to administer surfactant therapy 2 hours after birth. Analysis of blood gases and thoraco-abdominal X-ray showed clinical improvement and radiological evaluation following surfactant therapy (Figure 4).

Underdeveloped lungs in premature infants necessitate adequate respiratory monitoring. The third baby experienced recurrent desaturation and apnea, leading to the decision to intubate using Assist Control Volume Guarantee (AC-VG) ventilation method on the ninth day of treatment. The third baby was successfully extubated due to improved condition, and the frequency of desaturation decreased on the twelfth day.

Appropriate nutrition therapy is crucial in the management of premature infants. In the first three days, the total fluid administered to the babies ranged from 60-80 ml/kg body weight, and all infants received parenteral nutrition support consisting of Protein and Glucose (PG) 2-2.6 g, lipid 1-2 g, with a total calorie intake of 60.7 kcal/kg body weight. Parenteral nutrition was combined with trophic feeding using breast milk. After the first week, the amount of fluid, calories, and breast milk given to the patients increased. By the second week, all babies were receiving full breast milk feeds with the addition of human milk fortifier (HMF) and/or premature formula. The development of body weight, body length, and head circumference of the infants was routinely monitored using the Fenton premature infant growth chart for male infants (Figure 5). The progression of body weight based on Post Menstrual Age (PMA) is shown in Table 2.



A B C D

Figure 5. *Fenton Premature Growth Chart for Premature Infants, A. First Baby, B. Second Baby, C. Third Baby, D. Fourth Baby.*

Table 2. *Weight Monitoring Based on Post Menstrual Age (PMA).*

PMA	First	Second	Third	Fourth
29 + 0	1350	1370	1100	1195
29 + 5	1270	1235	1090	1164
30 + 6	1510	1530	1200	1350
31 + 5	1640	1603	1260	1508
32 + 2	1835	1660	1400	1671
32 + 5	1930	1800	1560	1772
32 + 6	2000	1930	1630	1800
33 + 1	2030	2070	1706	1820
33 + 2	2055	2095	1723	1850
33 + 5	2150	2150	1730	1930
33 + 6	2180	2175	1760	1955
34 + 0	2230	2220	1785	1995
34 + 2	2360	2290	1790	2030
34 + 6	2375	2305	1800	2095
35 + 5	2800	2660	1965	2180

PMA: Post menstrual age dalam minggu + hari
Third: Third Baby Body weight (gram)
First: First Baby Body weight (gram)
Fourth: Fourth Baby Body weight (gram)
Second: second Baby Body weight (gram)

During the course of treatment, all infants experienced hyperbilirubinemia that improved with phototherapy. Throughout the treatment period, all infants received packed red blood cell (PRC) transfusions due to anemia. The first baby received a transfusion on day 19 of treatment (Hb 11.1), the second baby on day 18 (Hb 11.1), the third baby on day 9 (Hb 13.2) and day 36 (Hb 9.8), and the fourth baby on day 28 (Hb 9.8). The third baby also experienced thrombocytopenia (platelet count 23,000) with suspected sepsis, and blood culture showed positive results for Enterobacter Cloacae. Consequently, the baby received antibiotics, platelet concentrate (TC), fresh frozen plasma (FFP), and a 1 mg vitamin K injection. Premature infants are susceptible to organ immaturity, necessitating comprehensive screening. All four babies were screened for retinopathy of prematurity (ROP) in the fourth week and screened for osteopenia of prematurity (OOP) and hearing in the fifth week, with results within normal limits.

The first baby was discharged from the Neonatal Intensive Care Unit (NICU) on day 37 of hospitalization with a post-menstrual age (PMA) of 34+1, the second baby was hospitalized for 45 days with a PMA of 35+3, the third baby was hospitalized for 37 days with a PMA of 34+1, and the fourth baby was hospitalized for 45 days with a PMA of 35+3. After discharge from the NICU, kangaroo care and Family-Centered Care (FCC) were implemented for the premature babies (Figure 6).

Figure 6. *Kangaroo mother care for premature babies.*

Our hospital implements care using the Family-Centered Care (FCC) approach for premature infant care. We consistently provide information and support to the families from the time of admission until discharge, regarding the infant's condition during treatment and the decisions and therapies implemented during the hospital stay. We believe that this approach offers benefits to both the parents, allowing them to feel more at ease, and to the well-being of the infants themselves (Figure 7).

Figure 7. *Family-Centered Care implemented for premature infants in our hospital.*

After considering the readiness of the infants and parents, the quadruplets were finally allowed to be discharged, accompanied by thorough education provided to the parents regarding further monitoring at the referring healthcare facility and appropriate nutrition for infants with a history of premature birth (Figure 8).

Figure 8. *The quadruplets and mother returning home in a healthy condition.*

3. Discussion

Although ovulation induction and in vitro fertilization treatments appear to dramatically increase the prevalence of multiple pregnancies, spontaneous quadruplet pregnancies are still very rare [7, 8]. In this case, the patient's mother had no history of assisted reproductive techniques and no family history of multiple pregnancies. The incidence of spontaneous quadruplet pregnancies ranges from one in 512,000 to one in 677,000 births and is associated with higher rates of maternal and neonatal mortality and morbidity [3]. According to Nnadi et al., pregnancies with more than two fetuses occur in 0.01% to 0.07% of all pregnancies. Obstetricians face difficulties in managing quadruplet pregnancies due to the increased challenges of pregnancy and delivery [8]. Pre-eclampsia, gestational diabetes, cardiac respiratory disorders, and premature labor are commonly encountered maternal issues in pregnancies with more than two fetuses.

Over 90% of births in pregnancies with more than two fetuses are premature [3]. Prematurity, which increases perinatal mortality and morbidity, is the primary consequence for the fetuses in pregnancies with more than two fetuses [9]. Twin babies typically have a gestational age of 35 weeks at birth, while triplets have an average gestational age of 32.2 weeks, and quadruplets have an average gestational age of 29.9 weeks. Less than 3% of pregnancies result in live-born quadruplets reaching full term [2]. Due to the high-risk nature of labor for both the mother and the babies, our team decided to terminate the pregnancy at 28 weeks. Another consideration was that the discovery of this quadruplet pregnancy requiring regular monitoring was only made at 7 months gestation due to the patient's low socioeconomic status and the remote location of her residence from healthcare facilities. Elective cesarean section was the recommended method of delivery for the quadruplet pregnancy, given the increased risk of fetal malpresentation and the challenges associated with intrapartum fetal monitoring [10].

Management of pregnancies with more than two fetuses requires special care and a multidisciplinary approach. Early involvement of neonatology experts and access to a Neonatal Intensive Care Unit (NICU) play a crucial role in achieving better outcomes. Preparations include resuscitation teams and NICU teams, as well as ensuring adequate resources for critical moments in premature infant resuscitation. In our first experience managing such a case, we prepared four neonatal resuscitation teams, each with four warming beds/resuscitation stations, T-resuscitators, and four sets of resuscitation equipment. Each team consisted of a pediatrician and a nurse to facilitate critical timing in the resuscitation of premature infants. The NICU team prepared the necessary equipment, beds, and medication, especially during the Golden Hour.

Nearly all premature neonates experience respiratory distress, necessitating appropriate and adequate respiratory support to maintain their breathing. The goal of respiratory management is to preserve vital functions, reduce iatrogenic injury, and optimize long-term outcomes. The choice of respiratory support varies based on the neonate's respiratory status, whether invasive ventilation modes or non-invasive ventilation modes are used. Invasive ventilation modes include Conventional Mechanical Ventilation (CMV) and High-Frequency Oscillation (HFO), while non-invasive respiratory support includes Continuous Positive Airways Pressure (CPAP), Non-Invasive Intermittent Positive Pressure Ventilation (nIPPV) or Bilevel Nasal CPAP (BiPAP), High-Flow Nasal Cannula (HFNC), and Low-Flow Nasal Cannula (LFNC) [11]. In our case, all premature babies required respiratory support to maintain adequate breathing. Not all babies required the same respiratory support, and the type of respiratory support given was tailored to each baby's respiratory status

Hyaline membrane disease (HMD), also known as neonatal respiratory distress syndrome, is one of the most common health problems affecting premature newborns [12]. HMD typically worsens within the first 48 to 72 hours [13, 14]. Clinical manifestations used to detect this condition include irregular breathing, flaring of the nostrils, chest wall retractions, and asynchronous chest and abdominal movements with or without cyanosis [15, 16].

In multivariate analysis, neonates experiencing asphyxia with a gestational age below 34 weeks or a birth weight below 1500 grams serve as predictors of HMD [12]. Compared to newborns with an APGAR score above seven, premature neonates with a 5-minute APGAR score below 7 are more likely to develop HMD [12, 17, 18]. Premature infants weighing less than 1500 grams have a 2.4-fold higher risk of respiratory problems compared to infants weighing more than 1500 grams [12]. In our case, all infants exhibited signs of HMD, with the second infant showing clinical deterioration due to more severe HMD and requiring surfactant therapy.

The administration of surfactant in premature infants with HMD reduces mortality rates, lowers the incidence of pneumothorax and interstitial lung emphysema, and decreases the risk of chronic lung disease or death at 28 days of age, according to a systematic review of randomized controlled trials [19]. We decided to administer early surfactant therapy (within the first two hours after birth) based on the grade III

HMD presentation observed through physical and radiological examinations. Early surfactant administration is associated with a significant reduction in mortality rates, a decrease in the incidence of bronchopulmonary dysplasia and mortality at 36 weeks, and a risk of air leaks, but not an increased risk of pulmonary hemorrhage or severe intraventricular hemorrhage, according to a meta-analysis of six randomized trials [10, 20]. In our case, after surfactant therapy, lung expansion showed improvement both clinically and in thoraco-abdominal X-ray evaluations.

Regarding weight, length, head circumference, organ size, tissue components including cell structure and count, blood and tissue nutrient concentrations, the nutritional goal for premature infants is to provide nutrition to meet the growth rate and body composition of a normal and healthy infant at the same gestational age [21]. Starting immediately after birth, increasing nutrition in very preterm newborns through intravenous (IV) and enteral feeding promotes good protein and energy balance and improves long-term neurodevelopmental outcomes [21]. The risk of retinopathy of prematurity (ROP) decreases when weight gain approaches that of a normally developing fetus [22]. We initiated nutrition delivery when resuscitation and stabilization during the golden hour were achieved, and our parenteral nutrition followed the guidelines of RSCM. In addition to parenteral nutrition, to achieve full feeding, we also provided enteral nutrition support in the form of breast milk and human milk fortifier (HMF). Several obstacles hindered the attainment of optimal nutrition delivery, such as differing respiratory and infection statuses of each infant.

Based on WHO recommendations for the care of preterm infants (<32 weeks) or very low birth weight (<1.5 kg), breastfeeding with breast milk is highly recommended. In cases where mothers have difficulty producing breast milk, donor breast milk may be considered. When breastfeeding and donor breast milk are not feasible, the use of preterm formula milk can be considered. Enteral feeding should be initiated as early as possible after birth. If breastfeeding is not possible initially, it should be introduced as soon as feasible. During hospitalization, WHO recommends scheduled feeding (every 2-3 hours with a volume of approximately 120-180 ml/kg/day) over responsive feeding, as responsive feeding can lead to poor growth and prolong hospital stay. For infants unable to breastfeed and requiring alternative feeding methods, the volume of breast milk/formula milk should be increased to a maximum of 30 ml/kg/day [23]. Maintaining respiratory support for infants is also crucial for their growth. Most premature infants require respiratory assistance to maintain breathing, and the use of continuous positive airway pressure (CPAP) is preferred over intubation. When hospitalized, maintaining closeness between the infant and parents, such as through skin-to-skin contact, can aid in neurobehavioral development [24]. WHO recommends CPAP therapy for premature infants presenting clinical symptoms of respiratory distress syndrome (RDS). Early CPAP initiation reduces the likelihood of intubation compared to delayed CPAP. For very preterm infants (<32 weeks), CPAP therapy is recommended after birth with or without RDS symptoms. Optimal management in neonates is still a subject of debate, including how and when to administer exogenous surfactant therapy. In cases of apnea, methylxanthines (caffeine) are recommended as therapy, with a loading dose of 20 mg/kg followed by a maintenance dose of 5 mg/kg for 6 weeks. If caffeine is unavailable, aminophylline or theophylline may be considered [23, 24]. In our case, during the first 3 days, all infants received parenteral nutrition with a total calorie intake of 60.7 kcal/kg body weight since enteral nutrition or breastfeeding was not feasible yet. Enteral nutrition was initiated after the first week with breast milk and additional preterm formula milk, with the amount gradually increasing after the second week. To maintain respiration, all infants used respiratory support, and due to clinical deterioration, the second infant underwent intubation and received surfactant therapy 2 hours after birth, showing clinical improvement. During the observation period, the third infant experienced repeated desaturation, leading us to decide to perform intubation on day 9, which subsequently showed clinical improvement.

Poor postnatal growth can occur due to the failure to meet protein and calorie requirements in infants, resulting in failure to thrive where the infant does not grow appropriately for their gestational age. To maintain growth rate in premature infants, several factors need to be considered, including the time required to achieve optimal daily intake (120 kcal/kg/day), the time required to achieve full feeding, and the time required to catch up with the weight appropriate for their gestational age. The goals of achieving optimal nutritional intake include maintaining linear growth according to the Fenton growth chart, achieving growth velocity with a minimum weight gain of 15-20 grams per day until 34 weeks, followed by 25-30 grams per day, a length increase of 0.9 cm per week, a head circumference increase of 0.9 cm per week, and being within the 10th-50th percentile by 7 months of age [25]. In our case, regarding growth velocity, the weight of infants 1, 2, and 4 was within the 10th-50th percentile, while infant 3 remained below the 10th percentile. Regarding length, only infants 2 and 3 were within the 10th-50th percentile, and all infants were within the 10th-50th percentile for head circumference.

Premature infants are catabolic during the first few days after birth, utilizing limited body stores and amino acids to maintain energy production at the expense of growth. Low nutrient supply, delayed enteral nutrition, and diabetes are some reasons why premature infants do not receive sufficient nutrition [21]. Since preterm infants are in a critical period of development, inadequate nutrition and the release of anabolic hormones (growth-promoting) in response result in growth failure and long-term neurological effects. Malnutrition is a serious issue in premature infants [26, 27].

We implemented family-centered care principles in the care of premature infants, which emphasizes the involvement

of the family in the care of the infant. Each family is unique, and the infant is influenced by family stress and their coping mechanisms, according to the principles of family-centered care [28, 29]. Meta-analysis research findings indicate that early intervention in the neonatal intensive care unit (NICU) combined with family-centered care reduces the risk of neonatal morbidity, such as prolonged oxygen use and moderate to severe bronchopulmonary dysplasia (BPD), and improves developmental outcomes in premature infants up to corrected age of 12 months [30].

4. Conclusion

Spontaneous quadruplet pregnancy is a rare occurrence, and this case represents the first experience of our hospital in managing quadruplet infants. A well-coordinated multidisciplinary approach, coupled with good preparedness for delivery, is absolutely necessary and has been shown to yield favorable outcomes for both the mother and infants.

Abbreviations

HMD	Hyaline Membrane Disease
PMA	Postmenstrual Age
G	Gender
MUAC	Mid Upper Arm Circumference (cm)
BW	Body Weight (gram)
APGAR	APGAR Scores at 1', 5'
BL	Body Length (cm)
TOB	Time of Birth
HC	Head Circumference (cm)
PEEP	Positive End Expiratory Pressure
MAP	Mean Airway Pressure

Author Contributions

All authors equally contributed to the implementation and preparation of this case report.

Funding

All authors declare that there was no external funding or grants associated with the writing of this case report.

Conflicts of Interest

The authors declare no conflicts of interest.

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