Role Of Vaginal Progesterone In Reducing Preterm Labour In Women With Short Cervix Identified In Mid Trimester Scan - Singleton Vs Twin Gestation: A Prospective Observational Comparative Study

Dr. Saritha Redishetty,
Sr Consultant, Dept Of Fetal Medicine, Fernandez Foundation, Hyderabad, Telangana, India

Dr. Sowmya Palaparthi
Senior Resident, Dept Of Obstetrics, Fernandez Foundation, Hyderabad, Telangana, India

Dr. Ravikanth Pula,
Professor, Dept Of Critical Care, ESIC Medical College, Hyderabad, Telangana, India

Dr. Geeta Kolar
Head and Sr Consultant, Dept Of Fetal Medicine, Fernandez Foundation, Hyderabad, Telangana, India
Dr.Suseela Vavilala
Sr Consultant, Dept Of Fetal Medicine, Fernandez Foundation, Hyderabad, Telangana, India

Abstract
Background
Preterm labor, especially in cases of short cervical length, is a major cause of neonatal morbidity and mortality. Vaginal progesterone has been recognized as an effective treatment to reduce preterm labor risk. However, its role in twin gestations needs further exploration.
Methods
This prospective observational comparative study was conducted at Fernandez Hospital, Hyderabad, from August 2020 to August 2021. Women with singleton and twin pregnancies diagnosed with a short cervix (cervical length <25mm) in the mid-trimester scan were administered vaginal progesterone (200 mg) daily, and their cervical lengths were monitored weekly. Primary outcomes included preterm labor incidence and neonatal outcomes.
Results
A total of 219 women were enrolled, with 146 in the singleton group and 73 in the twin group. The use of vaginal progesterone significantly reduced preterm births before 34 weeks in the singleton group compared to the twin group. NICU admissions and adverse neonatal outcomes were higher in the twin gestation group.
Conclusion
Vaginal progesterone is effective in lowering preterm labor risks in women with a short cervix, with better outcomes observed in singleton pregnancies compared to twin gestations.
Keywords: Preterm labor, vaginal progesterone, short cervix, singleton pregnancy, twin pregnancy, neonatal outcome.

I.Introduction

Preterm birth (PTB), defined as delivery before 37 weeks of gestation, remains a significant challenge in obstetrics and neonatal care. PTB is associated with substantial neonatal morbidity and mortality and poses a global health burden. According to the World Health Organization (WHO), an estimated 15 million babies are born prematurely each year. These early births account for approximately 1 million deaths annually, and many

survivors face lifelong complications, including respiratory disorders, intraventricular hemorrhage, and neurodevelopmental delays[1]. The burden is particularly high in low- and middle-income countries, where access to advanced neonatal care is often limited.

Several risk factors contribute to preterm birth, but cervical insufficiency is among the most prominent. Cervical length is a key indicator of preterm birth risk, with a cervical length of less than 25 mm—identified between 14 and 24 weeks—significantly increasing the likelihood of spontaneous PTB[2]. This association is well-established, and cervical insufficiency, characterized by painless dilation of the cervix, plays a crucial role in the onset of early labor[3].

Progesterone, an essential hormone in maintaining pregnancy, has been widely studied for its ability to inhibit uterine contractions and support cervical competence. Research has demonstrated that supplementation with vaginal progesterone significantly reduces the risk of preterm birth, particularly in women with a short cervix[4,5]. Despite this evidence, the majority of studies focus on singleton pregnancies, with limited research available on the effectiveness of vaginal progesterone in twin gestations[6–8]. Twin pregnancies inherently carry a higher risk of preterm birth due to mechanical factors, including uterine overdistention, which may limit the efficacy of progesterone therapy.

Given the known benefits of progesterone in preventing PTB in singleton pregnancies and the lack of conclusive evidence in twin pregnancies, this study aims to evaluate the efficacy of vaginal progesterone in reducing preterm labor in women with a short cervix. The study compares outcomes between singleton and twin pregnancies, providing further insight into the differential impact of progesterone therapy in these populations.

II.Materials And Methods

This prospective observational comparative study was conducted at Fernandez Hospital, a tertiary care center in Hyderabad, India, between August 2020 and August 2021. The hospital performs approximately 8,000 deliveries annually, providing a comprehensive setting for examining pregnancy outcomes in both singleton and twin gestations.

Study Design and Participants

The study was designed to assess the effectiveness of vaginal progesterone in preventing preterm birth in women with singleton and twin pregnancies diagnosed with a short cervix during their mid-trimester scan. Participants were recruited based on the following inclusion criteria: singleton or twin pregnancy, cervical length between 21–25 mm as identified by transvaginal ultrasound between 16–24 weeks of gestation, and willingness to use vaginal progesterone. Exclusion criteria included cervical length less than 20 mm, non-measurable cervix, structural or chromosomal fetal anomalies, polyhydramnios, complicated monochorionic twins (MCMA or MCDA), and severe maternal comorbidities such as hypertension or cardiac disease. Additionally, women opting for cerclage instead of progesterone therapy were excluded from the study.

A total of 219 women met the inclusion criteria and were enrolled in the study. Of these, 146 women had singleton pregnancies, and 73 had twin pregnancies, maintaining a 2:1 ratio. Participants were administered 200 mg of vaginal progesterone (suppository) daily from the time of short cervix detection until 36 weeks of gestation. Cervical length was monitored weekly using transvaginal ultrasound scans until 24 weeks of gestation. The scans were performed by trained fetal medicine consultants certified by the Fetal Medicine Foundation, ensuring accuracy and consistency in cervical length measurements.

Outcome Measures

The primary outcome of the study was the incidence of preterm birth, defined as delivery before 37 weeks of gestation. Secondary outcomes included gestational age at delivery, neonatal intensive care unit (NICU) admissions, neonatal mortality and morbidity, and birth weight. Additional outcomes included the frequency of tocolysis use and steroid administration for fetal lung maturity.

Data Collection and Analysis

Clinical data were collected from electronic medical records and ultrasound reporting software. Maternal demographics, obstetric history, mode of conception, cervical length, and pregnancy outcomes were recorded and analyzed.

The sample size was calculated using the formula proposed by Kirkwood et al., assuming the expected proportion of preterm births in twin pregnancies to be 60% and in singleton pregnancies to be 40%, with a power of 80% and a 5% two-sided alpha error. Based on these assumptions, a total of 219 participants were required, with 146 women in the singleton group and 73 women in the twin group.

The collected data were entered into Microsoft Excel and analyzed using SPSS version 25. Descriptive statistics were used to summarize demographic characteristics and clinical variables. Continuous variables, such as gestational age at delivery and cervical length, were presented as mean ± standard deviation (SD).

Categorical variables, such as the incidence of preterm birth and NICU admissions, were expressed as frequencies and percentages. The Independent Samples t-test was used for continuous variables, while the Chi-square test was employed for categorical variables. For continuous variables that did not follow a normal distribution, the Mann-Whitney U test was used. Correlation analyses were conducted to evaluate relationships between cervical length, gestational age, and neonatal outcomes. A p-value of <0.05 was considered statistically significant for all analyses.

III.Results

Among the 219 women who participated in the study, 146 had singleton pregnancies, and 73 had twin pregnancies. The two groups were comparable in terms of maternal age, body mass index (BMI), gravidity, and mode of conception. The mean maternal age was 28.7 years (±4.87) for the singleton group and 28.27 years (±4.82) for the twin group, with no statistically significant difference between the two groups (p = 0.479). Similarly, the BMI was comparable between the groups, with 65.1% of women in the singleton group and 56.2% in the twin group having a BMI between 25–29.99 kg/m² (p = 0.1476) **(Table 1)**.

Most women were diagnosed with a short cervix between 18–22 weeks of gestation in both groups (83.5% for singleton pregnancies and 85.1% for twin pregnancies), and there was no statistically significant difference in the gestational age at diagnosis between the groups. Further cervical shortening during surveillance was observed in 15.07% of singleton pregnancies and 16.4% of twin pregnancies, with no significant difference between the groups (p = 0.2701).

Preterm Birth and Gestational Age at Delivery **(Table 2,3& Figure 1)**

The mean gestational age at delivery was significantly higher in the singleton group compared to the twin group. Women with singleton pregnancies delivered at a mean gestational age of 36.5 weeks (±1.5 weeks), while those with twin pregnancies delivered at 35.4 weeks (±1.6 weeks) (p = 0.001).

Preterm deliveries before 34 weeks were more common in the twin group (15.1%) compared to the singleton group (11.6%), although this difference was not statistically significant (p = 0.11). However, preterm birth before 37 weeks was significantly more common in twin pregnancies (89.5%) compared to singleton pregnancies (86.4%) (p < 0.05).

Neonatal Outcomes **(Table 4)**

Birth weight was significantly lower in twin pregnancies compared to singleton pregnancies. In the singleton group, 76.7% of neonates had a normal birth weight (≥2,500 g), while in the twin group, only 1.4% of the first-born twin and 2.7% of the second-born twin had a normal birth weight. The incidence of low birth weight (<2,500 g) was significantly higher in twin pregnancies, with 57.5% of the first-born twin and 60.3% of the second-born twin classified as low birth weight, compared to 12.3% in the singleton group (p < 0.001).

NICU admissions were more frequent in twin pregnancies, particularly for the first-born twin **(Figure 2)**. In the singleton group, 17.1% of neonates required NICU admission, compared to 34.2% of first-born twins and 19.2% of second-born twins. The difference in NICU admissions between singleton neonates and first-born twins was statistically significant (p = 0.0022), but there was no significant difference between singleton neonates and second-born twins (p = 0.7079).

Neonatal mortality was higher in the twin group, particularly for the first-born twin**(Table 5)**. In the singleton group, 4.8% of neonates did not survive, compared to 17.8% of first-born twins and 6.8% of second-born twins. The neonatal death rate for first-born twins was significantly higher than that of singleton neonates (p = 0.04164).

The take-home baby rate (surviving neonates discharged from the hospital) was 95.2% in the singleton group, 82.2% in the first-born twin group, and 93.2% in the second-born twin group **(Table 6)**. The take-home baby rate was significantly lower in the first-born twin group compared to the singleton group (p = 0.000). However, the difference between the singleton group and the second-born twin group was not statistically significant (p = 0.2644)

IV.Discussion

This study aimed to investigate the impact of vaginal progesterone in reducing preterm labor in women with short cervical lengths, focusing on differences in outcomes between singleton and twin pregnancies. The findings suggest that while vaginal progesterone is effective in decreasing the incidence of preterm birth (PTB) in both groups, its efficacy is significantly greater in singleton pregnancies.

The improved outcomes in singleton pregnancies observed in this study align with previous research. For example, the OPTIMUM trial[7,8] reported a similar mean gestational age of 36.9 weeks in singleton pregnancies receiving vaginal progesterone, closely matching the 36.5 weeks seen in this study. Additionally, the proportion of preterm births before 34 weeks (11.6%) in this study is comparable to the 10.7% rate noted in

meta-analyses on the effectiveness of vaginal progesterone in singleton pregnancies with short cervix. Numerous randomized controlled trials (RCTs)[9] have confirmed that progesterone therapy effectively prolongs pregnancy in singleton gestations.

In contrast, the effectiveness of vaginal progesterone in twin pregnancies is more limited. In this study, twin pregnancies showed some improvements with progesterone treatment, but the outcomes were less favorable than those observed in singleton pregnancies. The mean gestational age at delivery for twin pregnancies was 35.4 weeks, and 15.1% of these pregnancies delivered before 34 weeks. Although these results represent an improvement compared to untreated twin pregnancies, they are still suboptimal compared to singleton outcomes. This pattern of reduced efficacy in twin gestations has been highlighted in various meta-analyses and systematic reviews[5,9–15].

The underlying reasons for the diminished effectiveness of progesterone in twin pregnancies likely stem from uterine overdistention and other mechanical and inflammatory factors unique to multiple gestations[5]. Progesterone's ability to suppress uterine contractions may not be sufficient to counteract these forces. Additionally, the functional withdrawal of progesterone receptors, especially in the context of twin pregnancies, may further reduce the effectiveness of the hormone in preventing preterm labor.

The study also found that twin pregnancies had significantly higher rates of NICU admissions[16,17], low birth weight (LBW), and neonatal mortality compared to singleton pregnancies. The take-home baby rate, or the proportion of neonates discharged alive from the hospital, was notably lower in the twin group, particularly for the first-born twin. This underscores the greater risks associated with twin pregnancies, even with progesterone treatment.

Strengths and Limitations

A strength of this study is its prospective design, which allowed for the close monitoring of cervical length and the regular assessment of progesterone's efficacy. The comparison between singleton and twin pregnancies provides valuable insights into the differing impacts of progesterone treatment on these populations. Furthermore, the study's adherence to a standardized protocol for cervical length measurement adds to the reliability of the findings.

However, there are certain limitations to this study. The smaller sample size for twin pregnancies may have limited the statistical power to detect significant differences in some outcomes. Moreover, the study was conducted at a single tertiary care center, which may limit the generalizability of the findings to other populations. Future studies with larger sample sizes and conducted across multiple centers are needed to confirm these results and explore additional interventions for twin pregnancies.

V.Conclusion

Vaginal progesterone is an effective intervention for reducing preterm birth risk in women with singleton pregnancies and a short cervix. In twin gestations, however, the benefit is limited, underscoring the need for further research and potential alternative therapies to enhance neonatal outcomes.

Conflict of interest: No conflict of interest
Acknowledgement: Nil

Reference:

(1) Ndonyi, J. Utilization Of Free Skilled Birth Attendance Services Among Women Of Reproductive Age In Public Health Facilities In Kitui County, Kenya. Front Neurosci 2021, 14 (1).

(2) Erratum To: Cervical Length For Predicting Preterm Birth And A Comparison Of Ultrasonic Measurement Techniques (Australasian Journal Of Ultrasound In Medicine, (2013), 16, 3, (124-134), 10.1002/J.2205-0140.2013.Tb00100.X). Australasian Journal Of Ultrasound In Medicine. 2013. Https://Doi.Org/10.1002/J.2205-0140.2013.Tb00251.X.

(3) Thain, S.; Yeo, G. S. H.; Kwek, K.; Chern, B.; Tan, K. H. Spontaneous Preterm Birth And Cervical Length In A Pregnant Asian Population. Plos One 2020, 15 (4). Https://Doi.Org/10.1371/Journal.Pone.0230125.

(4) Erratum: Department Of Error (The Lancet (2021) 397(10280) (1183–1194), (S0140673621002178), (10.1016/S0140-6736(21)00217-8)). The Lancet. 2021. Https://Doi.Org/10.1016/S0140-6736(21)00827-8.

(5) Murray, S. R.; Stock, S. J.; Cowan, S.; Cooper, E. S.; Norman, J. E. Spontaneous Preterm Birth Prevention In Multiple Pregnancy. The Obstetrician & Gynaecologist 2018, 20 (1). Https://Doi.Org/10.1111/Tog.12460.

(6) Romero, R.; Conde-Agudelo, A.; El-Refaie, W.; Rode, L.; Brizot, M. L.; Cetingoz, E.; Serra, V.; Da Fonseca, E.; Abdelhafez, M. S.; Tabor, A.; Perales, A.; Hassan, S. S.; Nicolaides, K. H. Vaginal Progesterone Decreases Preterm Birth And Neonatal Morbidity And Mortality In Women With A Twin Gestation And A Short Cervix: An Updated Meta-Analysis Of Individual Patient Data. Ultrasound In Obstetrics And Gynecology. 2017. Https://Doi.Org/10.1002/Uog.17397.

(7) Norman, J. E.; Marlow, N.; Messow, C. M.; Shennan, A.; Bennett, P. R.; Thornton, S.; Robson, S. C.; Mcconnachie, A.; Petrou, S.; Sebire, N. J.; Lavender, T.; Whyte, S.; Norrie, J. Vaginal Progesterone Prophylaxis For Preterm Birth (The Opptimum Study): A Multicentre, Randomised, Double-Blind Trial. The Lancet 2016, 387 (10033). Https://Doi.Org/10.1016/S0140-6736(16)00350-0.

(8) Romero, R.; Nicolaides, K. H.; Conde-Agudelo, A.; O'brien, J. M.; Cetingoz, E.; Da Fonseca, E.; Creasy, G. W.; Hassan, S. S. Vaginal Progesterone Decreases Preterm Birth ≤ 34 Weeks Of Gestation In Women With A Singleton Pregnancy And A Short Cervix: An Updated Meta-Analysis Including Data From The Opptimum Study. Ultrasound Obstet Gynecol 2016, 48 (3).

Https://Doi.Org/10.1002/Uog.15953.

(9)   Rode, L.; Klein, K.; Nicolaides, K. H.; Krampl-Bettelheim, E.; Tabor, A. Prevention Of Preterm Delivery In Twin Gestations (Predict): A Multicenter, Randomized, Placebo-Controlled Trial On The Effect Of Vaginal Micronized Progesterone. Ultrasound In Obstetrics And Gynecology 2011, 38 (3). Https://Doi.Org/10.1002/Uog.9093.

(10) Schuit, E.; Stock, S.; Rode, L.; Rouse, D. J.; Lim, A. C.; Norman, J. E.; Nassar, A. H.; Serra, V.; Combs, C. A.; Vayssiere, C.; Aboulghar, M. M.; Wood, S.; Çetingöz, E.; Briery, C. M.; Fonseca, E. B.; Worda, K.; Tabor, A.; Thom, E. A.; Caritis, S. N.; Awwad, J.; Usta, I. M.; Perales, A.; Meseguer, J.; Maurel, K.; Garite, T.; Aboulghar, M. A.; Amin, Y. M.; Ross, S.; Cam, C.; Karateke, A.; Morrison, J. C.; Magann, E. F.; Nicolaides, K. H.; Zuithoff, N. P. A.; Groenwold, R. H. H.; Moons, K. G. M.; Kwee, A.; Mol, B. W. J. Effectiveness Of Progestogens To Improve Perinatal Outcome In Twin Pregnancies: An Individual Participant Data Meta-Analysis. Bjog: An International Journal Of Obstetrics And Gynaecology. 2015. Https://Doi.Org/10.1111/1471-0528.13032.

(11) Eddama, O.; Petrou, S.; Regier, D.; Norrie, J.; Maclennan, G.; Mackenzie, F.; Norman, J. E. Study Of Progesterone For The Prevention Of Preterm Birth In Twins (Stoppit): Findings From A Trial-Based Cost-Effectiveness Analysis. Int J Technol Assess Health Care 2010, 26 (2). Https://Doi.Org/10.1017/S0266462310000036.

(12) Norman, J. E.; Mackenzie, F.; Owen, P.; Mactier, H.; Hanretty, K.; Cooper, S.; Calder, A.; Mires, G.; Danielian, P.; Sturgiss, S.; Maclennan, G.; Tydeman, G.; Thornton, S.; Martin, B.; Thornton, J. G.; Neilson, J. P.; Norrie, J. Progesterone For The Prevention Of Preterm Birth In Twin Pregnancy (Stoppit): A Randomised, Double-Blind, Placebo-Controlled Study And Meta-Analysis. The Lancet 2009, 373 (9680). Https://Doi.Org/10.1016/S0140-6736(09)60947-8.

(13) Brizot, M. L.; Hernandez, W.; Liao, A. W.; Bittar, R. E.; Francisco, R. P. V.; Krebs, V. L. J.; Zugaib, M. Vaginal Progesterone For The Prevention Of Preterm Birth In Twin Gestations: A Randomized Placebo-Controlled Double-Blind Study. Am J Obstet Gynecol 2015, 213 (1). Https://Doi.Org/10.1016/J.Ajog.2015.02.021.

(14) Roeckner, J. T.; Mitta, M.; Sanchez-Ramos, L.; Kaunitz, A. M. 552: Twin Pregnancies With Short Cervix: Vaginal Progesterone Is Agent Of Choice For Preterm Delivery Prevention. Am J Obstet Gynecol 2019, 220 (1). Https://Doi.Org/10.1016/J.Ajog.2018.11.574.

(15) Conde-Agudelo, A.; Romero, R.; Rehal, A.; Brizot, M. L.; Serra, V.; Da Fonseca, E.; Cetingoz, E.; Syngelaki, A.; Perales, A.; Hassan, S. S.; Nicolaides, K. H. Vaginal Progesterone For Preventing Preterm Birth And Adverse Perinatal Outcomes In Twin Gestations: A Systematic Review And Meta-Analysis. American Journal Of Obstetrics And Gynecology. 2023. Https://Doi.Org/10.1016/J.Ajog.2023.05.010.

(16) Kilicarslan, N.; Gurbuz, H.; Tasgoz, F. N.; Karaca, U.; Karasu, D.; Gamli, M. Factors Influencing Neonatal Outcomes In Twin Pregnancies Undergoing Cesarean Section: A Cross-Sectional Study. Rev Assoc Med Bras 2023, 69 (5). Https://Doi.Org/10.1590/1806-9282.20221464.

(17) Bellizzi, S.; Sobel, H.; Betran, A. P.; Temmerman, M. Early Neonatal Mortality In Twin Pregnancy: Findings From 60 Low- And Middle-Income Countries. J Glob Health 2018, 8 (1). Https://Doi.Org/10.7189/Jogh.08.010404.

Tables And Figures
Table 1: Baseline Characteristics of the Study Population

Characteristic	Singleton (%)	Twins (%)	p-value
Age Group (years)			
< 20	1.4	2.7	0.479
21–30	53.4	63.0	
31–40	44.5	32.9	
> 40	0.7	1.4	
Mean Age (years)	28.7 (±4.87)	28.27 (±4.82)	
BMI (kg/m²)			
18–24.99	28.1	28.7	0.1476
25–29.99	65.1	56.2	
>30	6.1	15.1	
Gravidity			
G1	43.2	39.7	0.1090
G2	26.0	37.0	
G3+	30.8	23.3	

Table 2: Gestational Age at Delivery and NICU Admissions

Parameter	Singleton (%)	Twins (%)	p-value
Gestational Age at Delivery (weeks)			
< 28	0.7	1.4	0.9054
28–31.6	2.7	2.7	
32–34.6	11.6	15.1	
35–36.6	72.6	71.2	
> 37	12.4	9.6	
NICU Admission			
Yes	17.1	34.2 (First Twin)	0.0022
		19.2 (Second Twin)	0.7079

Table 3: Mean GA at Delivery and Cervical Length at Diagnosis

Parameter	Singleton (Mean ± SD)	Twins (Mean ± SD)
Mean Age (years)	28.7 ± 4.871	28.27 ± 4.825

Mean Gestational Age at Delivery (weeks)	36.5 ± 1.5	35.4 ± 1.6
Mean Cervical Length in mm	23± 1.3	21± 1.1

Table 4: Neonatal Outcomes (Birth Weight and APGAR Scores)

| Parameter	Singleton (%)	First Twin (%)	Second Twin (%)	p-value
Birth Weight				
Normal Weight	76.7	1.4	2.7	<0.001
Low Birth Weight	12.3	57.5	60.3	
Very Low Birth Weight	6.2	37.0	32.9	
Extremely Low Birth Weight	4.8	4.1	4.1	
APGAR Score (1 minute)				
< 4 (Severe Depression)	0.7	0.0	0.0	0.0256
4–7 (Mild Depression)	17.1	32.9	19.2	
> 7 (No Depression)	82.2	67.1	80.8	

Table 5: Neonatal deaths among babies admitted to NICU in singleton and twin pregnancies

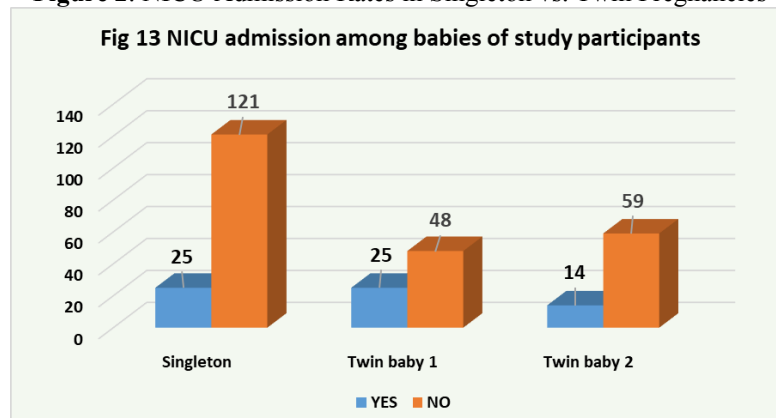| Neonatal death	Singleton No. (%)	First twin baby No. (%)	Second twin baby No. (%)
Yes	07 (28.0)	13 (52.0)	05 (35.7)
No	18(72.0)	12 (48.0)	09 (64.3)
Total	25 (100)	25 (100)	14 (100)
Chi-square (Singleton Vs first twin baby and Singleton Vs second twin baby) and p-value		x^2 = 2.082 p 0.04164	x^2 =0.2509 p 0.3083

Table 6: Overall Take-home baby (THB-live babies) rates in singleton and twin pregnancies

Outcome	Singleton No. (%)	First twin baby No. (%)	Second twin baby No. (%)
Neonatal death	07 (04.8)	13 (17.8)	05 (06.8)
Survived	139 (95.2)	60 (82.2)	68 (93.2)
Total	146 (100)	73 (100)	73 (100)
Chi-square (Singleton Vs first twin baby and Singleton Vs second twin baby) and p-value		x^2= 9.932 p 0.000	x^2= 0.3967 p 0.2644

Figure 1: Gestational Age at Delivery in Singleton vs. Twin Pregnancies

Fig 10 Gestational age (in weeks) at delivery of study participants (x^2=1.029 p 0.9054)
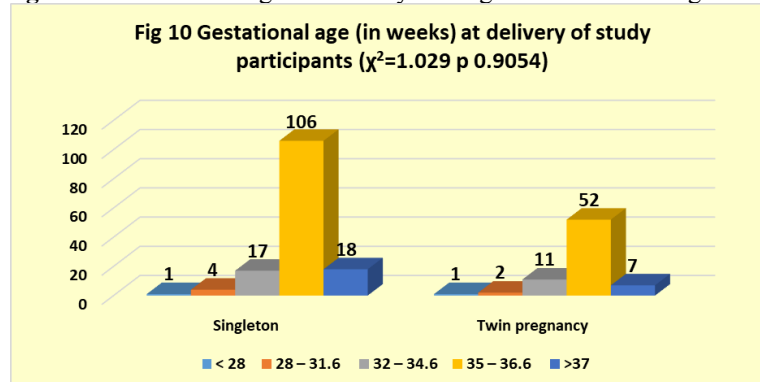
Figure 2: NICU Admission Rates in Singleton vs. Twin Pregnancies

Fig 13 NICU admission among babies of study participants

Bar chart showing NICU admission rates, comparing singleton neonates and the first- and second-born twins.