Original Article

Optimal gestational age for delivery in uncomplicated dichorionic twin pregnancies: a population-based study

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Abstract

Objectives: To identify the optimal gestational age for delivery in uncomplicated dichorionic twin pregnancies.

Study Design: A retrospective analysis of gestational age-specific neonatal morbidity and mortality data was performed for 254 uncomplicated dichorionic twin pregnancies. Outcome measures included 1st and 5th minute Apgar scores, NICU admission, RDS, TTN, sepsis, seizure, hyperbilirubinemia, hypoglycaemia, neonatal length of hospital stay, birthweight and overall outcome. After correcting for confounding variables by regression analysis, adverse variable trends were assessed in each of the gestational-age-at-birth groups.

Results: A significant drop in the incidence of LBW, RDS, TTN and hypoglycaemia, accompanied with the lowest NICU admission rate and neonatal length of hospital stay occurred concordantly at 38 completed weeks of gestation. The incidence of severe hyperbilirubinemia requiring phototherapy decreased significantly by 36 weeks. No correlation was found between advancing gestation and foetal, perinatal or neonatal mortality.

Conclusion: Elective delivery in uncomplicated dichorionic twin pregnancies should be delayed until at least 38 completed weeks of gestation as this significantly reduces neonatal morbidity with no impact on mortality.

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Twins, Pregnancy, Outcome

Introduction

In recent years, multiple pregnancy has been on the rise secondary to a delay in childbearing age and more widespread use of assisted reproductive technology.[1-2] Records show that twin births in the Maltese islands have increased from 1.04% in the 1960-1969 period, when the use of ART was presumably minimal, to 1.51% in 2015.[3]

Twin pregnancies are associated with increased fetal, perinatal and neonatal risks and complications when compared to their singleton counterparts. This is attributable to the higher incidence of preterm birth, lower birth weight and the associated physiological instability and lung immaturity of the infant.[4-6]

Preterm birth is a leading cause of death and complications in the neonatal period and one of the key causes for poor developmental outcomes in childhood.[7] Gestational age at delivery is thus a key factor affecting neonatal outcome in twin pregnancies.[8-9] Appropriate timing for delivery of twin pregnancies is a matter of acknowledging the dynamic balance that exists between in-utero foetal stillbirth risk and ex-utero neonatal risk.[10]

In general, clinical practice guidelines regarding the optimal gestational age of delivery in uncomplicated dichorionic twin pregnancies favour delivery in the early-term period (37^{+0}-38^{+6} weeks). A consensus opinion from a 2011 workshop held by the Society for Materno-foetal Medicine (SMFM) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

suggests delivery at 38 weeks of gestation for uncomplicated dichorionic twins and 34 to 37 weeks for uncomplicated monochorionic diamniotic twins.[11] The National Institute for Health and Clinical Excellence (NICE) recommends elective delivery of dichorionic twin pregnancies from 37 weeks of gestation and monochorionic twin pregnancies from 36 weeks (after a course of corticosteroids).[12] The American College of Obstetricians and Gynaecologists (ACOG) recommends delivery of uncomplicated dichorionic twins at 38^{+0} to 38^{+6} weeks and uncomplicated monochorionic twins at 34^{+0} to 37^{+6} weeks of gestation.[13-14]

Although several investigators have undertaken studies to define the optimal delivery time for twin pregnancy, some results are controversial due to lack of chorionicity data and the confounding effect of pre-pregnancy or pregnancy-induced conditions on neonatal morbidity, mortality or the decision for delivery. This study deals solely with uncomplicated dichorionic twin pregnancies. It eliminates the confounding effect of relatively higher risk monochorionic pregnancies as well as eliminating the effect that maternal comorbidities, pregnancy-induced conditions and congenital anomalies have on the obstetric decision for delivery and outcome. These exclusion criteria allow for clearer inquiry into the interplay between gestational age and neonatal outcome variables. Such a consideration should drive the empowerment of both obstetricians and parents towards more informed decision-making when balancing the risks and benefits of discretionary delivery.

Methods

Population-based retrospective data for all twin deliveries occurring in the Maltese islands in the 2008-2014 period was obtained from the National Obstetric Information System (NOIS) database. Systematic neonatal data collection for NOIS commences from the point of delivery and lasts until discharge from hospital or until 28 days of neonatal life.

Exclusion criteria were applied to the data sequentially, eliminating births that occurred prior to 34 weeks of gestation, as well as excluding neonates with major congenital anomalies as defined by the European Registration of Congenital Anomalies (EUROCAT). Pregnancies involving maternal chronic ill health and pregnancy-induced conditions including gestational hypertension, gestational diabetes, pre-eclampsia, and intrauterine growth restriction were excluded. Growth restriction was defined as birthweight below the 10^{th} percentile for gestational age or inter-twin weight discordance of more than 20%.

To ensure exclusion of monochorionic pregnancies only twin deliveries with clear documentation of chorionicity data (separate gestational sacs / lambda sign in ultrasound scans done up to 14 weeks of gestation) or different sex at birth were included.

Data collection concerning neonatal outcome included 1^{st} and 5^{th} minute Apgar scores, admission to the neonatal intensive care unit (NICU), perinatal morbidity (respiratory distress syndrome (RDS), transient tachypnoea of the newborn (TTN), sepsis, seizure, hyperbilirubinemia, hypoglycaemia), neonatal length of hospital stay, birthweight and overall outcome (perinatal death and early/late neonatal death). Variables that represented potential confounders included maternal age, parity, smoking, alcohol intake, drug abuse, antenatal maternal steroid administration, twin birth order and infant sex.

Valid data entries were allocated into gestational-age-at-birth groups, starting from 34^{+0}-34^{+6} weeks and continuing upwards at one week intervals. Regression models were built up using gestational age and neonatal outcome variables, and forward stepwise regression was applied to eliminate the confounding effect of risk factors that were initially found to also have a significant effect on the dependant outcome variable. Statistical analysis was done using the IBM SPSS Statistics package Version 22 and Microsoft Excel 2013. Ethical approval was acquired from the University of Malta University Research Ethics Committee on 16^{th} November 2015.

Results

In the period studied (2008-2014), there were 29,497 deliveries and 474 twin sets. Out of the 474 twin sets, 254 pairs met the inclusion criteria. These mothers had a mean maternal age of 30.6 years (95%CI 30.21-30.99), 53.43% of which were primiparous women.

The highest proportion of deliveries occurred by elective caesarean section (CS) at 37 and 38 completed weeks of gestation. (*Figure 1*) The

majority of deliveries prior to 37 weeks of gestation were via CS after the onset of spontaneous labour or rupture of membranes (ROM).

Figure 2 depicts a logistic-function pattern of birthweight gain with advancing gestation. The birthweight of twin neonates born to non-smoking mothers was found to be 148.60 grams higher (95%CI 28.50-268.70g) than twin neonates of smokers ($p<0.005$).

Male infant birthweight was a mean 90.26 grams ($p<0.0009$, 95% CI 37.22-143.31g) higher than female infants. The percentage proportion of twin neonates with LBW (<2500g) was highest at 35 weeks of gestation, decreasing linearly to 35.20% and 26.28% at 37 and 38 weeks respectively (*Figure 3*).

***Figure 1**: Mode of delivery of twin neonates according to gestational age at birth*

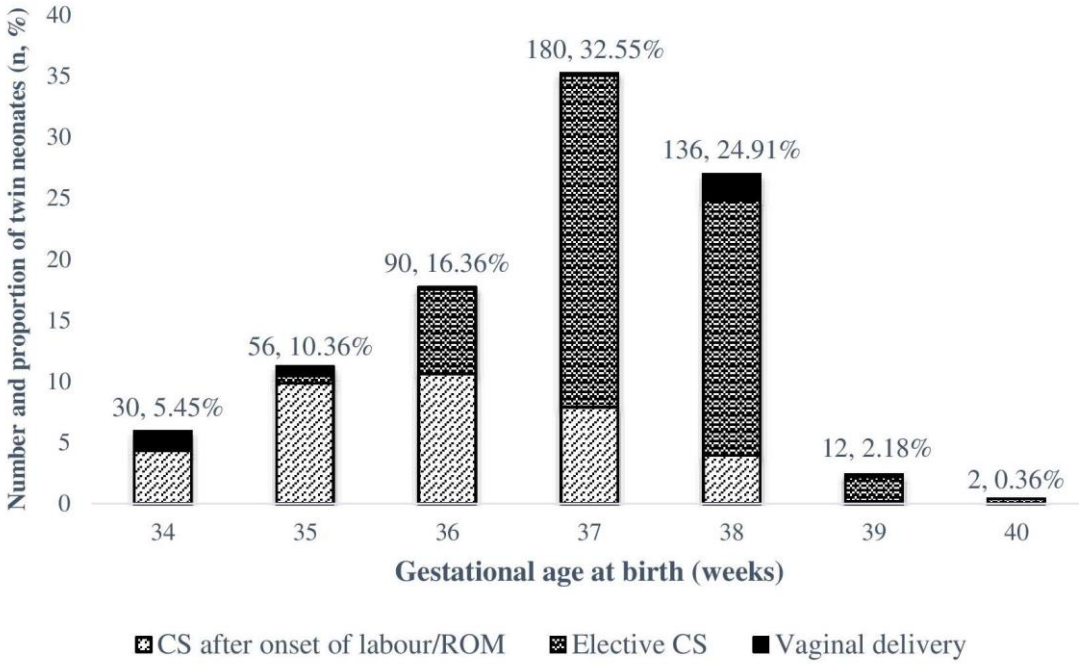


***Figure 2:** Mean birthweight according to gestational age at delivery in uncomplicated dichorionic twin pregnancies*

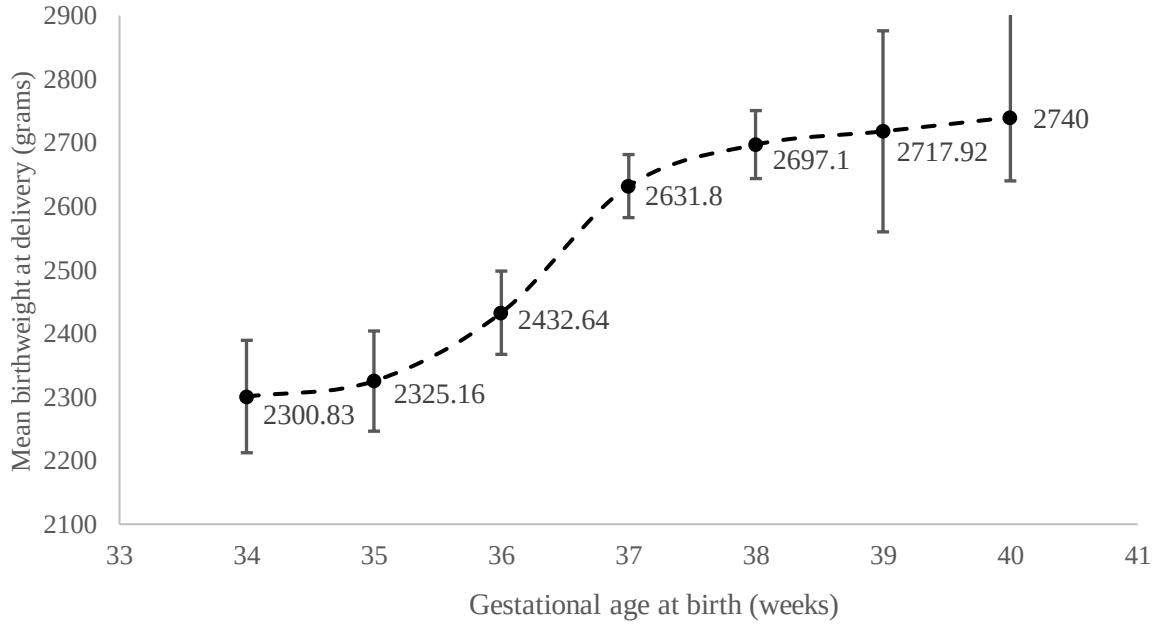


Figure 3: *Incidence of LBW (1500g-2499g) in twin neonates according to gestational age at birth*

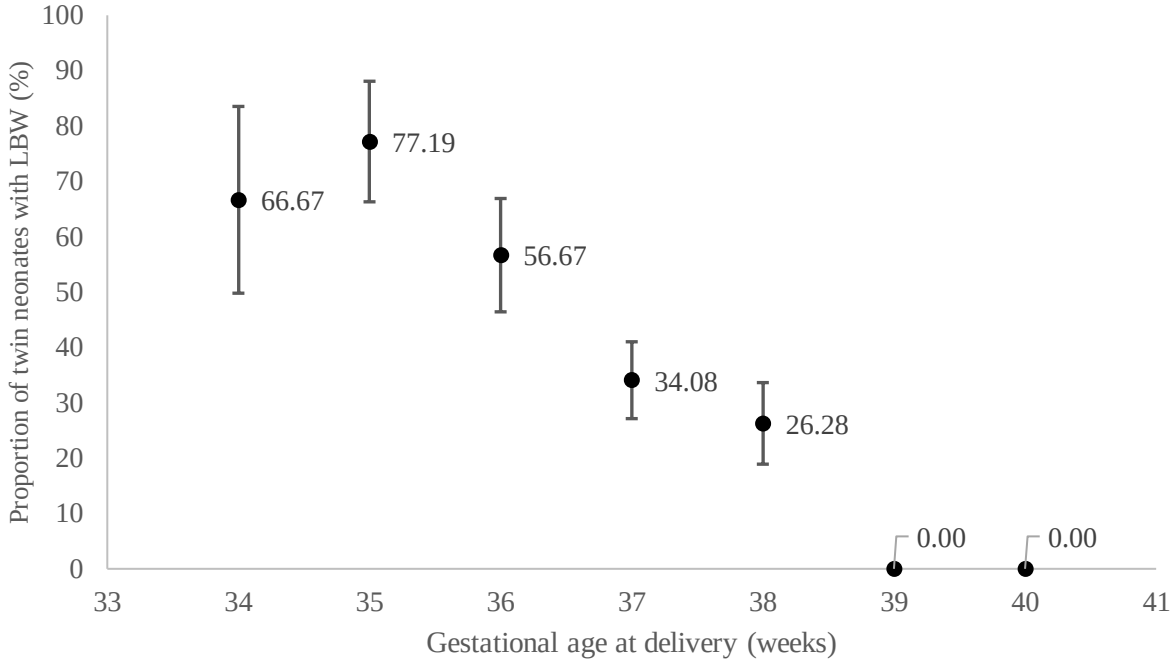
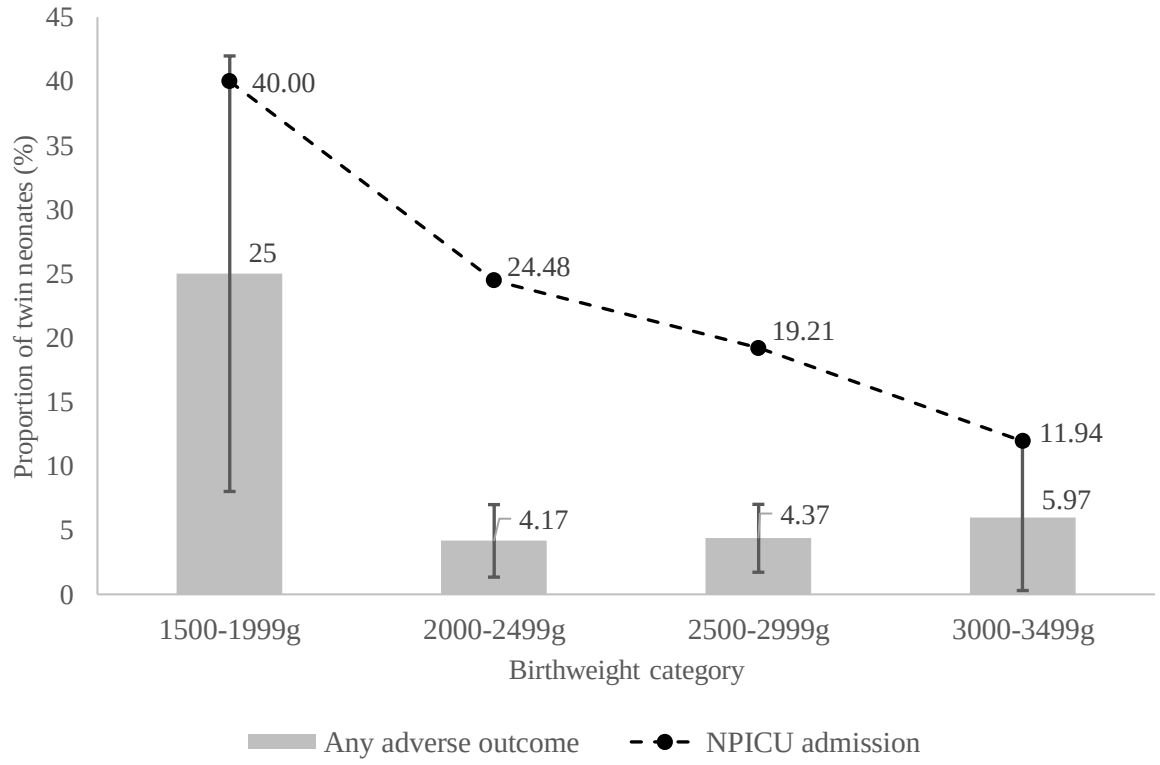


Figure 4: *Incidence of any adverse outcome (RDS, TTN, 1st/5th Apgar <7, Hyperbilirubinemia, Hypoglycaemia or Sepsis) and NICU admission according to birthweight category*



LBW was associated with RDS (RR 3.00 95%CI 1.63-5.50, $p<0.0001$), hypoglycaemia (RR 4.65 95%CI 1.30-16.71, $p=0.009$) and intensive care requirement (RR 1.48 95%CI 1.06-2.07 $p=0.02$). (*Figure 4*).

The mean first minute Apgar score was significantly higher in neonates born at 39 or 40 completed weeks of pregnancy. This intergroup difference was no longer detected at the fifth minute. (*Figure 5*)

RDS affected 9.45% of the twin cohort. There was a sharp statistically significant drop in the incidence of RDS at 38 completed weeks of gestation with only 1.46% being diagnosed ($p<0.001$). The incidence of RDS decreased significantly as gestational age increased, each additional week of gestation after 34 weeks decreasing the risk of RDS by 57.10% ($p<0.001$, 95%CI 45.13-72.38).

Figure 5: *Mean 1st (blue) and 5th minute (red) Apgar score according to gestational age of dichorionic twin neonates*

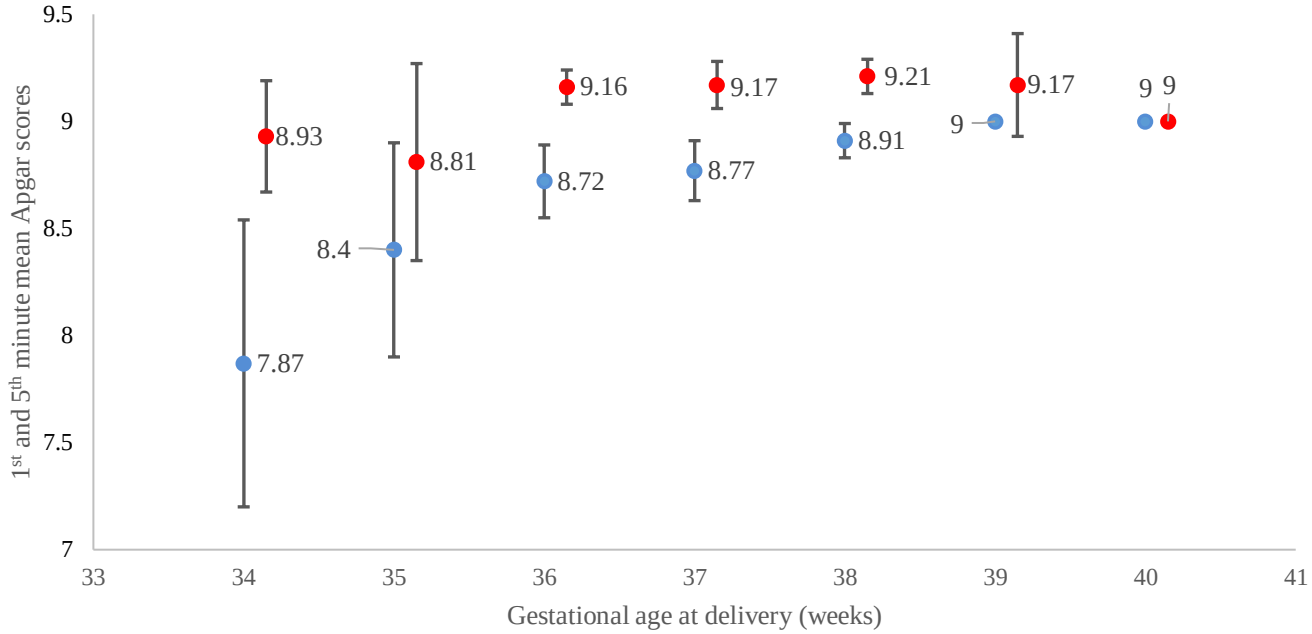


Figure 6: *Percentage of twin neonates affected by RDS according to gestational age at delivery*

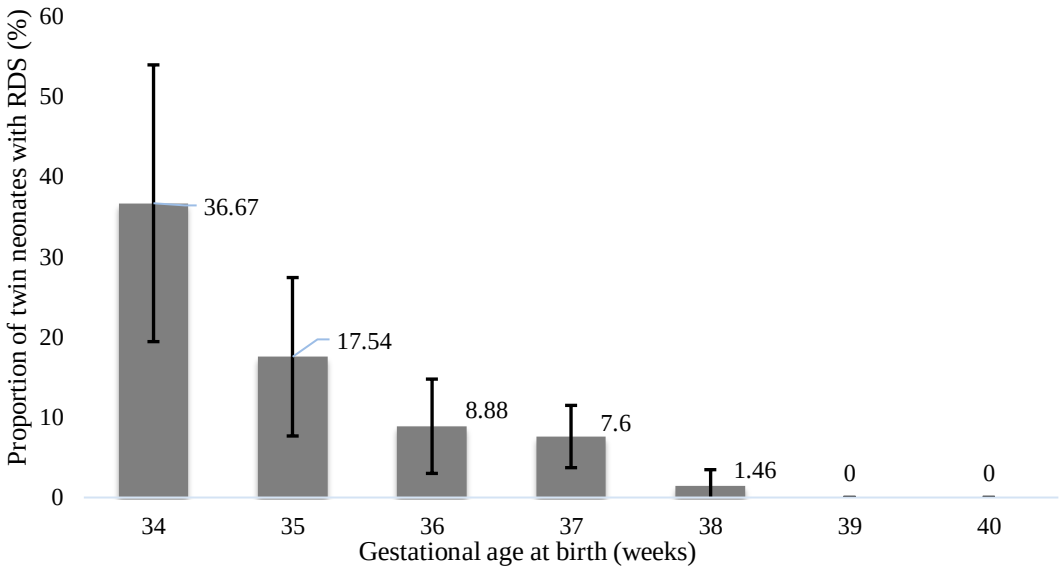


Figure 7: *Percentage of twin neonates affected by TTN according to gestational age at delivery*

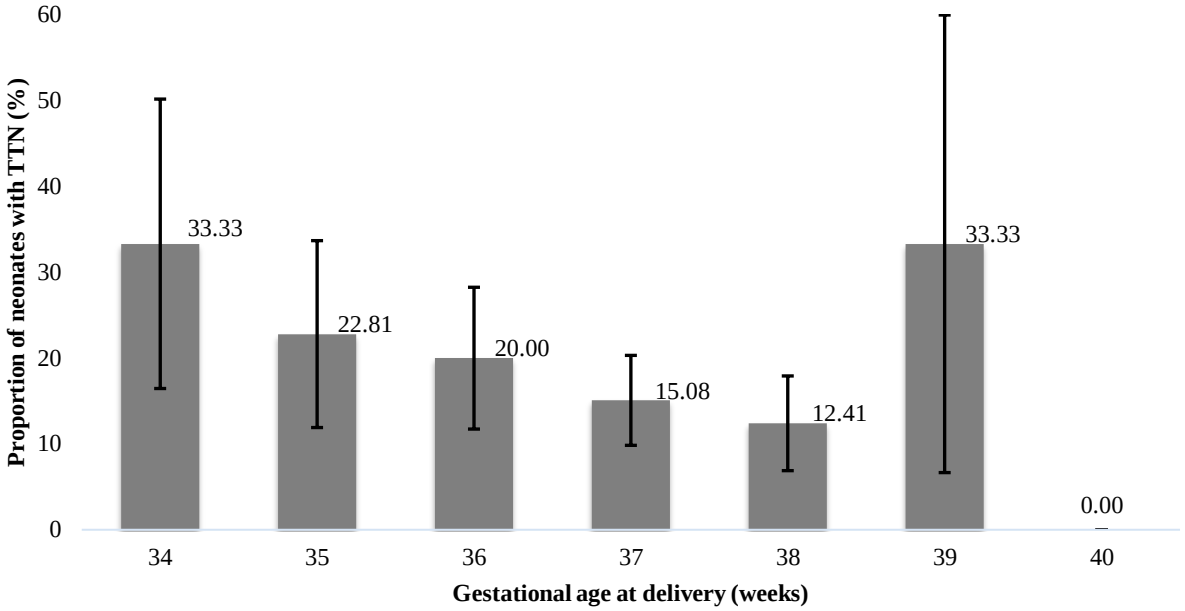
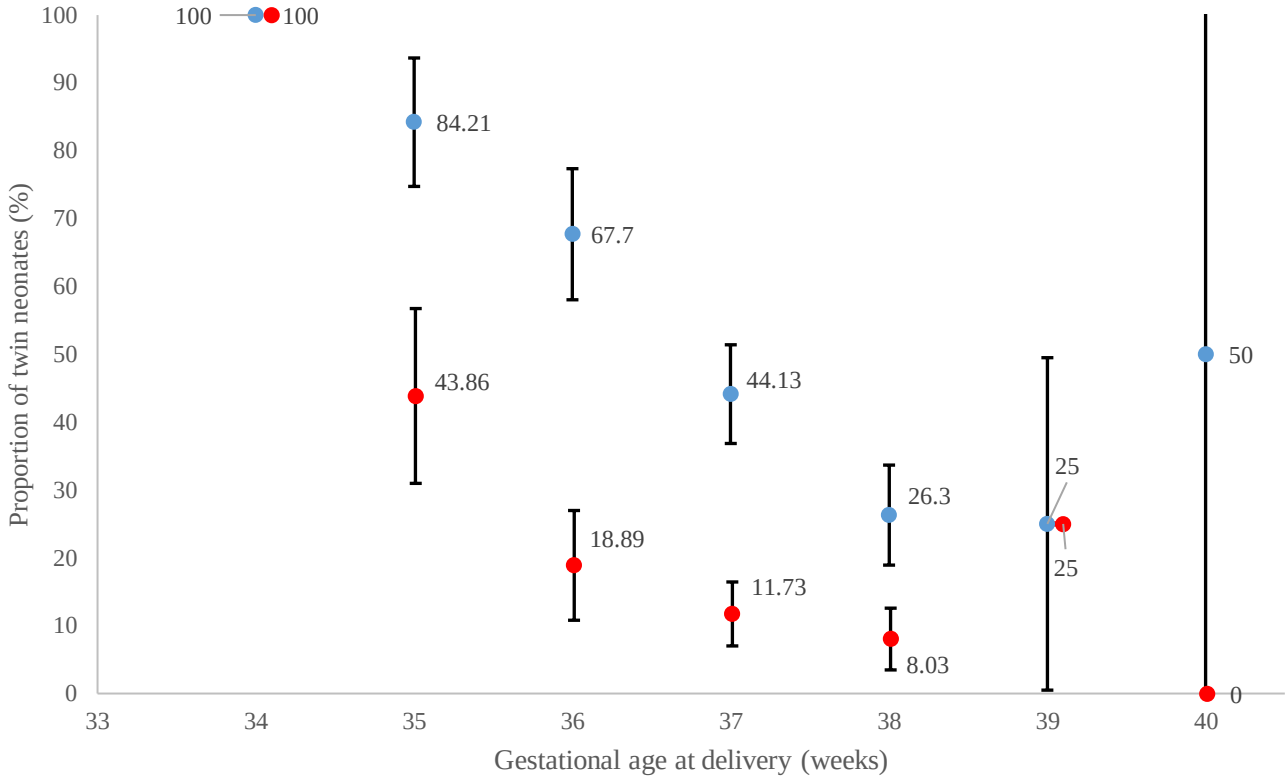


Figure 8: *Proportion of twin neonates with at least one adverse outcome (blue) and NICU admission (red) according to gestational age at birth*



The proportion of twin neonates with TTN also decreased with advancing gestation. Each additional week of gestation from 34 weeks onwards decreased the risk of TTN by 22.51% (p<0.001, 95%CI 12.33-55.21). A considerable but non-significant rise in TTN was observed at 39 weeks gestation. (*Figure 7*)

A total of seven neonates had hyperbilirubinemia that necessitated phototherapy. The highest proportion of neonates requiring phototherapy were born at 34 completed weeks of gestation, followed by a significant reduction from 36 weeks onwards. Prevalence of hypoglycaemia decreased gradually, with no cases reported at 38 weeks gestation. There were no recorded neonatal seizures in the studied cohort and no significant trends in sepsis rates were detected.

All neonates born at up to 34^{+6} weeks of gestation were admitted to NICU for a period of observation due to departmental policy. NICU admission rate was lowest in neonates born at early term (37^{+0}-38^{+6} weeks). Each additional week of gestation beyond 34 weeks decreased NICU admission rate by 43.88% (p<0.001, 95%CI 38.10-50.51). A considerable but non-significant rise in NICU admission rate occurred at 39 weeks gestation. The trend for mean neonatal length of stay in hospital is dependent on and follows the pattern of gestational age-specific NICU admission rates.

On evaluation of the different gestational age at birth groups and the incidence of *any* adverse neonatal outcome (RDS, TTN, 1st or 5th minute Apgar <7, hyperbilirubinemia requiring phototherapy, sepsis, hypoglycaemia), a significant reduction in overall morbidity at 38 weeks of gestation was noted (*Figure 8*). This coincides with a nadir in NICU admission rate and neonatal length of hospital stay.

Discussion

During the period under study, overall twin pregnancies amounted to a mean 67.7 per year. 254 of these were dichorionic twin pregnancies which satisfied our inclusion criteria; a mean 40.7 pregnancies per year. Uncomplicated dichorionic twin pregnancies thus represent a small but noteworthy proportion of pregnancies at this state hospital.

A large proportion of twin neonatal complications are related to low birth weight and respiratory problems, namely RDS. This study identified an inverse association between birthweight and RDS, hypoglycaemia and intensive care requirement. Low birthweight implies metabolic instability in the neonate as well as a higher body surface area to volume ratio that makes the newborn susceptible to heat loss and hypothermia. There were no very low birthweight infants in this study population. This is because of the lower gestational age cut-off of 34 weeks, coupled with the exclusion of twin neonates with intrauterine growth restriction.

With a 5% mortality rate, RDS can be severe, however it becomes less common in infants born at 33 to 36 weeks of gestation and is rare in full-term infants.[15-16] The observed trends in RDS incidence reflect the different stages of foetal lung development. Remarkable changes in lung appearance begin at around the 28th week of gestation, when there is a decrease in interstitial tissue, and airspace walls become narrow and more compact. As reflected in the drop in RDS incidence at 36 completed weeks of gestation, alveoli then start appearing. From then onwards, during the saccular stage, the surfactant-secreting Type 2 pneumocytes are formed and the foetal ex-utero morbidity decreases significantly.

In general, RDS rates in our study population were higher than those in published literature. In a prospective study over 2 years, Bakr AF et al identified an RDS rate of 7% in deliveries at 36^{+0}-36^{+6} weeks and 0.8% at 37^{+0}-38^{+6} gestational weeks.[17] These investigators excluded maternal risk factors and congenital anomalies however included pregnancy-related conditions such as PIH and GDM. In our study, despite excluding these high-risk pregnancies, RDS rates at 36, 37 and 38 completed weeks were still marginally greater at 7.8, 8.4 and 1.5% respectively.

An important reason for this incongruity is the higher caesarean section (CS) rate in our local population, with 56.10% undergoing elective CS and another 38.58% undergoing CS after the onset of labour or ROM. This represents a total 94.68% of cases as opposed to 44.67% in Bakr AF et al's cohort.[17] Gerten KA et al reported that at any given gestational age, the incidence of RDS is greater for infants born by CS, especially without established labour, than for those born by vaginal delivery.[18] This could be due to a combination of delayed expulsion of pulmonary fluid and a lack of the

cortisol response associated with spontaneous labour.[19]

In our cohort, the incidence of RDS in neonates at 38 completed weeks of gestation was significantly lower than those born at 37 weeks. This benefit, and its secondary impact on NICU admission and neonatal length of hospital stay supports delaying delivery to 38 completed weeks whenever possible.

Within the CS subgroup we found that elective caesarean delivery was associated with a decreased age-adjusted risk of RDS (RR 0.79, $p<0.04$) and an increased risk of TTN (RR 2.21, $p<0.04$) when compared to CS after onset of labour/ROM. This observation may be secondary to information bias. Since surgery occurred electively with no suspected foetal prematurity or distress, hospital staff may have been more likely to label respiratory symptoms as TTN rather than RDS. A prospective study with strict diagnostic criteria would clarify this observation.

Hyperbilirubinemia in preterm infants is also more prevalent, more severe, and its course is more protracted than in term neonates.[20-22] Our findings are in keeping with those by Sarici SU et al[23] who studied 365 neonates and found that late preterm infants had a higher incidence of hyperbilirubinemia than those at 38 to 43 weeks gestation. There are numerous reasons for this observation. Primarily, there is an increased bilirubin load in hepatocytes as a result of decreased erythrocyte survival, higher erythrocyte volume, and increased enterohepatic circulation of bilirubin. In addition, a delay in the initiation of enteral feedings, which is common in the clinical management of sick premature newborns, may limit intestinal flow and bacterial colonisation resulting in further enhancement of bilirubin enterohepatic circulation.[24] In our study population severe hyperbilirubinemia was most prevalent in those born at 34 and 35 weeks, decreasing to almost nil from 36 weeks onwards.

Gestational age-specific NICU admission rates have been widely studied as these give a general picture of the neonate's condition at birth and physiological maturity. In a study by Lee HJ et al[25] the nadir of composite morbidity rate was observed at ≥39 weeks of gestation, where there was no NICU admission, neonatal morbidity or mortality. Lee HJ's study is a retrospective analysis of 18 years' worth of data on uncomplicated dichorionic twin pregnancies. Very similar data was obtained from the prospective cohort study by Bakr AF et al[17], with NICU rates decreasing significantly to 4.5% at early term (37^{+0}-38^{+6}) and to 0% at 39 completed weeks. Similarly, local NICU admission rates were lowest in neonates born at 37 and 38 weeks with a non-significant increase at 39 weeks of gestation. A wide confidence interval at this gestation reflects the data group's susceptibility to the effect that aberrant single data entries could have on the variable mean.

Any attempt to identify the optimal gestational age of delivery must counterbalance the neonatal benefits of advancing gestation with any possible increase in foetal/neonatal mortality risk. Luke B et al[26] concluded that there is a U-shaped pattern of mortality with the best outcomes observed at birth weights of 2,500-2,799g and 35-38 weeks gestation. This late surge in mortality beyond 38 weeks, they concluded, reflected the combined influence of growth retardation and advancing gestation on mortality. Over the seven year period under study we identified two stillbirths and no perinatal or neonatal deaths. These stillbirths occurred at 35 weeks gestation. This gave our study population a prospective intrauterine foetal death risk of 0.39% beyond 34^{+0} weeks. Unlike Luke B et al's study which included cases with maternal or pregnancy induced complications, this study did not identify a mortality surge in twin neonates at term.

Conclusion

Local population-based data suggests that in the absence of complication, dichorionic twin neonates continue to benefit from advancing gestation to at least 38 weeks with no consequence on foetal, perinatal or neonatal mortality. Delaying discretionary delivery to 38 weeks of gestation decreases the prevalence of LBW, RDS, TTN and hypoglycaemia while decreasing NICU admission rate and neonatal length of hospital.

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