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## BMJ Paediatrics Open

**Multicentre prospective observational study of feeding practices in 30–33 weeks preterm infants**

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2017-000040
Article Type:	Original article
Date Submitted by the Author:	19-Apr-2017
Complete List of Authors:	Kwok, T'ng Chang; University of Nottingham, Academic Divison of Child Health Ojha, Shalini; University of Nottingham, Academic Child Health Dorling, Jon; Queen's Medical Centre, Neonatal Unit
Keywords:	Nutrition, Infant Feeding, Neonatology

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Multicentre prospective observational study of feeding practices in 30–33 weeks preterm infants

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Word count (excluding title page, abstract, references, figures and tables): 1186 words

Keywords: nutrition, infant feeding, neonatology

**ABSTRACT****Background**

Current evidence supports progressive feeding in preterm infants. Due to lower necrotising enterocolitis risk, recent studies suggest starting total enteral feeding from birth in 30–33 weeks preterm infants. The feasibility of this practice is unclear.

**Aim**

Explore feeding practices in 30–33 weeks preterm infants.

**Design**

Prospective, multicentre, observational study recruiting ten consecutive 30–33 weeks preterm infants from eight UK hospitals.

**Results**

Eighty infants received their first feed at median of 24 hours, achieving total and full feeds at median of 5 and 8 days, respectively. Eleven infants who achieved total enteral feeding within 24 hours after birth achieved full feeds earlier ( $p=0.02$ ) with shorter hospital stay ( $p=0.009$ ) but were also of older gestation.

**Conclusion**

Current early feeding approaches in 30–33 weeks preterm infants were found to be conservative. Total enteral feeding from birth is possible in these infants but further studies are needed.

(148 words)

**KEY MESSAGES**

**"What is known about the subject":**

- Recent evidence suggests that earlier and rapid enteral feeding could be achieved in very preterm infants without increasing risk of necrotising enterocolitis or death.
- Compared to extremely preterm infants, there are fewer studies investigating enteral feeding practices in 30–33 weeks preterm infants who have lower necrotising enterocolitis risk.
- Two Indian studies found total enteral feeding from birth in 30–33 weeks preterm infants to be feasible and beneficial.

**"What this study adds"**

- Half the infants were fed on day 1, achieving total enteral (without intravenous nutrition) and full feeds ( $\geq 150\text{ml/kg/day}$ ) by day 5 and 8, respectively.
- Eleven infants who achieved total enteral feeding by day 1 achieved full feeds earlier ( $p=0.02$ ) with shorter hospital stay ( $p=0.009$ ) but were of older gestation.
- Total enteral feeding from birth is potentially feasible in 30–33 weeks preterm infants in the UK but further studies are needed.

## INTRODUCTION

A decision has to be made about how to feed every baby admitted for neonatal care. Conservative approaches have developed in an attempt to prevent necrotising enterocolitis (NEC) but recent meta-analyses have shown that earlier (1) and rapid (2) enteral feeding can be achieved in very preterm infants without increasing the risk of necrotising enterocolitis (NEC) or death. However, these studies concentrate on extremely preterm infants. There are very few studies investigating the early feeding of 30–33 weeks preterm infants, who have a lower risk of NEC, and represent nearly a fifth of preterm infants.

Two studies in India (3, 4) found the provision of total enteral feeding from birth in 30–33 weeks preterm infants to be feasible. Total enteral feeding from birth was defined as providing infants with exclusive enteral feeds without administering intravenous fluids. Infants given enteral feeds alone had improved feed tolerance, shorter hospital stays and reduced intravenous nutrition usage. However, the feasibility of this practice in the UK is uncertain.

## AIM

We aimed to explore current feeding practices in 30–33 weeks preterm infants in the UK as well as associated mortality and morbidity (NEC and late-onset sepsis (LOS)).

## METHODS

Prospective, multicentre observational study, in ten consecutive 30+0 to 33+6 weeks preterm infants, born and cared for in each of the 8 participating UK neonatal units from July–August 2016. Infants were excluded if they had conditions that made enteral feeding unsafe (e.g. trachea-oesophageal fistula). Feeding data were collected until full feeds was achieved (defined as  $\geq 150$  ml/kg/day for 3 days). Total enteral feeding was defined as receiving only enteral feeds without

any intravenous nutrition. LOS was defined as sepsis presenting >72 hours after birth requiring ≥5 days of intravenous antibiotics. NEC was defined as condition meeting the Stage 2 or 3 of the modified Bell’s criteria.

Categorical and continuous data were presented as number of infants (percentage) and median (Interquartile range, IQR) respectively. Growth parameters were presented as mean ± standard deviation (SD) with Z scores calculated using LMSgrowth 2012 (<http://www.healthforallchildren.co.uk/>). A priori analyses by gestational age and whether total enteral feeding was achieved within 24 hours after birth were performed. Mann-Whitney and chi-squared tests were used to compare continuous and categorical data, respectively. The Jonckheere-Terpstra test was used to compare trends among medians of multiple groups with an ordered pattern.

**RESULTS**

**Demographics**

Eighty infants were recruited from seven lead (Birmingham, Bristol, King’s College London, Leeds, Newcastle, Nottingham and Sheffield) and one local (Worcestershire) units. The median (IQR) gestational age was 32+3 (31+1–33+0) weeks and mean (SD) for birthweight as well as head circumference were 1728 (382) g and 29.3 (1.9) cm, respectively. There were 41 (51%) males, 5 (13%) sets of twins, and 1 (4%) set of triplets. One infant died and her data up to day of death had been included.

**Enteral feeding practices**

Infants received their first feed at a median (IQR) of 24 (11–43) hours of age. Forty-two (53%), two (3%) and thirty-two (40%) infants received maternal breastmilk, donor breastmilk and formula milk, respectively as their first feed. The type of milk received was not specified in 4 (5%) infants. Waiting for breastmilk was reported as the reason for delay in starting feeds in 43 (54%) infants (**Table 1**).

**Table 1: Reason reported for the delay in starting enteral feeds from birth in eighty 30 – 33 weeks preterm infants in the multicenter prospective observational study.**

\* Infants may have more than one reason.

Reason*	Number of Infants (%)
Waiting for breastmilk	43 (54%)
Respiratory distress needing non-invasive ventilation	10 (13%)
Absent umbilical artery end diastolic flow on antenatal scans	5 (6%)
Not tolerating feeds	4 (5%)
Hypoglycaemia needing intravenous fluids	3 (4%)
Respiratory distress requiring invasive ventilation	3 (4%)
Small for gestational age	2 (3%)
High lactate	2 (3%)
Others	4 (5%)

Feeds were increased at a median (IQR) rate of 24 (17–32) ml/kg/day, achieving full feeds on a median (IQR) of 8 (6–11) days. A median (IQR) of 5 (2–9) days of intravenous nutrition was given. Thirty-one (39%) infants had central venous access.

### Outcome

79 infants survived to discharge from hospital which was at a median (IQR) of 26 (16–39) days. Two (3%) infants developed NEC. One infant, from a set of twins born at 31+5 weeks gestation died at 5 days of age. She was enterally fed up to 45ml/kg/day on day 3 when she developed stage 3 NEC. The other was an infant born at 30+1 weeks gestation who developed Stage 2 NEC at 14 days of age after tolerating full enteral feeds for four days. His NEC was managed conservatively.



The z-score for weight for gestational age in 79 infants; and head circumference for gestational age in 60 infants changed by  $-0.7 \pm 0.8$  and  $0.1 \pm 1.8$  from birth to discharge. There were nine (11%) cases of LOS including four (5%) with positive blood or CSF cultures.

**A priori analyses**

*Gestation*

Higher gestational age at birth was associated with infants receiving the first ( $p<0.001$ ), total ( $p<0.001$ ), and full feeds earlier ( $p<0.001$ ), as well as shorter hospital stay ( $p<0.001$ ). (**Figure 1**).

*Total enteral feeding within 24 hours after birth*

Eleven (14%) infants achieved total enteral feeds within 24 hours after birth. They were of higher gestation compared to those who were not totally enteral fed by 24 hours (33 vs 32 weeks,  $p=0.004$ ). They also achieved full feeds earlier (5 vs 8 days,  $p=0.02$ ) and had shorter admissions (18 vs 30 days,  $p=0.009$ ).

**DISCUSSION**

Two randomised trials (3, 4) have suggested that it is possible to achieve total enteral feeds from birth in 30–33 weeks preterm infants. However, these reports, with very small numbers, are from India where the healthcare setting is very different and the preterm population may not be representative of that in the UK. However, the risk of NEC is very low in infants above 30 weeks gestation and other emerging evidence supports early progressive feeding. (1, 2) Despite this, we found that only half of our consecutive sample of 80 infants from 8 UK neonatal units received their first feed by day 1 and total enteral feeds without any intravenous nutrition by day 5. Ninety percent of the cohort received their first feed by 55 hours and achieved total enteral feeds by 13 days of age.

Non-availability of breastmilk was reported to cause delay in starting feeds in half of the infants, raising the question of whether alternative milks such as donor breastmilk or formula milk should be utilised in this period or whether it is better to wait for maternal breastmilk. Studies to date are inconclusive and heterogeneity among the studies makes the evidence difficult to assess. (5)

Our study found that infants who were totally enteral fed within 24 hours after birth achieved full feeds earlier with shorter hospital stays without statistical differences in death, NEC or LOS. However, our study was limited by a small sample size and the results were likely to be confounded by gestational age. Mature infants were more likely to be given total enteral feeding, tolerate milk feeds, and be discharged sooner with lower risk of complications. An adequately powered randomised controlled trial is needed to assess whether providing total enteral feeding from birth in 30–33 weeks preterm infants improves outcomes and reduces hospital stay without increasing the risk of NEC in the UK.

## CONCLUSION

Our study found that the feeding approach in 30–33 weeks preterm infants in the UK to be conservative. Total enteral feeding from birth is potentially feasible in these infants but further trials are needed before a change in practice can be recommended.

## ACKNOWLEDGMENTS

We would like to thank Dr Gillian Preston and Dr Gemma Holder (Birmingham Women's Hospital), Catherine Turner and Dr Paul Mannix (Southmead Hospital), Dr Ann Hickey (King's College, London), Dr Alex Liu and Dr Kathryn Johnson (Leeds General Infirmary), Dr Stefan Zalewski and Dr Nicholas Embleton (Royal Victoria Infirmary), Dr Rebecca Musson and Dr Tamanna Williams (Jessop Wing,

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**COMPETING INTEREST**

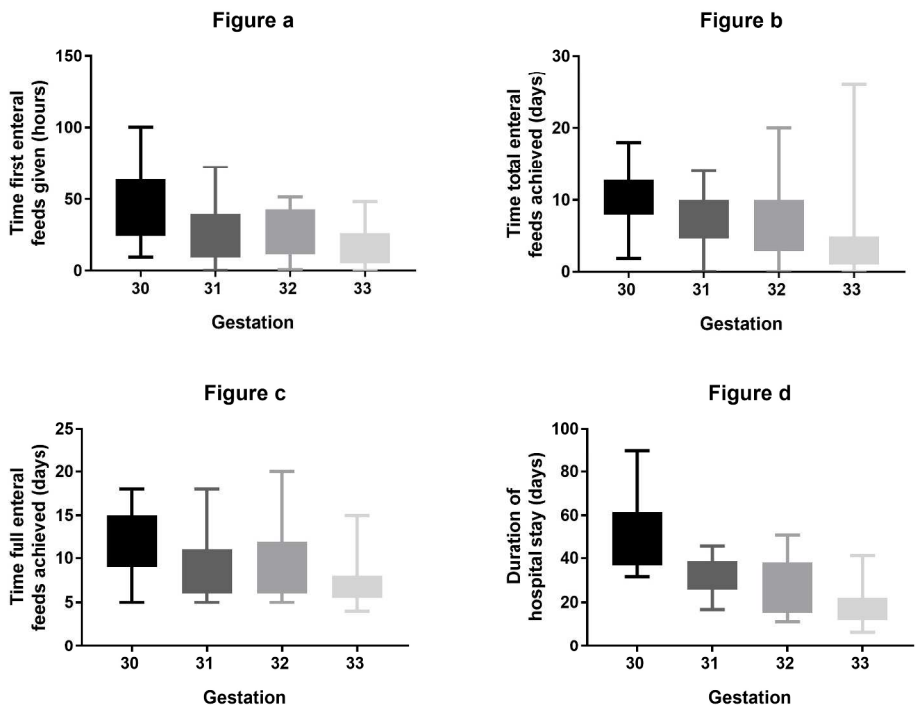
None declared.

**FUNDING**

None declared.

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258x196mm (300 x 300 DPI)

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Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2017-000040.R1
Article Type:	Original article
Date Submitted by the Author:	14-Jun-2017
Complete List of Authors:	Kwok, T'ng Chang; University of Nottingham, Academic Divison of Child Health Ojha, Shalini; University of Nottingham, Academic Child Health Dorling, Jon; Queen's Medical Centre, Neonatal Unit
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**Word count (excluding title page, abstract, references, figures and tables):** 1520 words

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Current early feeding approaches in 30–33 weeks preterm infants were found to be conservative. Total enteral feeding from birth is possible in these infants but further studies are needed.

(148 words)

**KEY MESSAGES**

**"What is known about the subject":**

- Recent evidence suggests that earlier and rapid enteral feeding could be achieved in very preterm infants without increasing risk of necrotising enterocolitis or death.
- Compared to extremely preterm infants, there are fewer studies investigating enteral feeding practices in 30–33 weeks preterm infants who have lower necrotising enterocolitis risk.
- Two Indian studies found total enteral feeding from birth in 30–33 weeks preterm infants to be feasible and beneficial.

**"What this study adds"**

- Half the infants were fed on day 1, achieving total enteral (without intravenous nutrition) and full feeds ( $\geq 150\text{ml/kg/day}$ ) by day 5 and 8, respectively.
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A decision has to be made about how to feed every baby admitted for neonatal care. Conservative approaches have developed in an attempt to prevent necrotising enterocolitis (NEC) but recent meta-analyses have shown that earlier (1) and rapid (2) enteral feeding can be achieved in very preterm infants without increasing the risk of necrotising enterocolitis (NEC) or death. However, these studies concentrate on extremely preterm infants. There are very few studies investigating the early feeding of 30–33 weeks preterm infants, who have a lower risk of NEC, and represent nearly a fifth of preterm infants.

Two studies in India (3, 4) found the provision of total enteral feeding from birth in 30–33 weeks preterm infants to be feasible. Total enteral feeding from birth was defined as providing infants with exclusive enteral feeds without administering intravenous fluids. Infants given enteral feeds alone had improved feed tolerance, shorter hospital stays and reduced intravenous nutrition usage. However, the feasibility of this practice in the UK is uncertain.

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We aimed to explore current feeding practices in 30–33 weeks preterm infants in the UK as well as associated mortality and morbidity (NEC and late-onset sepsis (LOS)).

## METHODS

Prospective, multicentre observational study, in ten consecutive 30+0 to 33+6 weeks preterm infants, born and cared for in each of the 8 participating UK neonatal units from July–August 2016. Infants were excluded if they had conditions that made enteral feeding unsafe (e.g. trachea-oesophageal fistula). Feeding data were collected until full feeds was achieved (defined as  $\geq 150$  ml/kg/day for 3 days). Total enteral feeding was defined as receiving only enteral feeds without

any intravenous nutrition. LOS was defined as sepsis presenting >72 hours after birth requiring ≥5 days of intravenous antibiotics. NEC was defined as condition meeting the Stage 2 or 3 of the modified Bell’s criteria.

No ethical approval was sought as this was purely an observational study exploring feeding practices in 30–33 weeks preterm infants in eight neonatal units across the UK. There was no new intervention proposed as part pf the study. Each participating unit was advised to register the work with their local audit department.

Categorical and continuous data were presented as number of infants (percentage) and median (Interquartile range, IQR) respectively. Growth parameters were presented as mean ± standard deviation (SD) with Z scores calculated using LMSgrowth 2012 (<http://www.healthforallchildren.co.uk/>). A priori analyses by gestational age and whether total enteral feeding was achieved within 24 hours after birth were performed. Mann-Whitney and chi-squared tests were used to compare continuous and categorical data, respectively. The Jonckheere-Terpstra test was used to compare trends among medians of multiple groups with an ordered pattern.

**RESULTS**

**Demographics**

Eighty infants were recruited from seven lead (Birmingham, Bristol, King’s College London, Leeds, Newcastle, Nottingham and Sheffield) and one local (Worcestershire) units. The median (IQR) gestational age was 32+3 (31+1–33+0) weeks and mean (SD) for birthweight as well as head circumference were 1728 (382) g and 29.3 (1.9) cm, respectively. There were 41 (51%) males, 5

(13%) sets of twins, and 1 (4%) set of triplets. One infant died and her data up to day of death had been included.

### Enteral feeding practices

Infants received their first feed at a median (IQR) of 24 (11–43) hours of age. Forty-two (53%), two (3%) and thirty-two (40%) infants received maternal breastmilk, donor breastmilk and formula milk, respectively as their first feed. The type of milk received was not specified in 4 (5%) infants. Waiting for breastmilk was reported as the reason for delay in starting feeds in 43 (54%) infants (**Table 1**).

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Others	4 (5%)

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Thirty-one (39%) infants had central venous access.

### Outcome

79 infants survived to discharge from hospital which was at a median (IQR) of 26 (16–39) days. Two (3%) infants developed NEC. One infant was from a set of twins born at 31+5 weeks gestation

weighing just below the 25<sup>th</sup> centile for birthweight. She was predominantly fed with formula milk up to 45ml/kg/day on day 3 when she developed stage 3 NEC. Her NEC was diagnosed based on surgical findings on day 3 of age. Unfortunately, she died 2 days later. Her twin brother was born just above the 25<sup>th</sup> centile for birthweight. He did not develop NEC despite being managed similarly.

The other was an infant born at 30+1 weeks gestation, weighing 50<sup>th</sup> centile for birthweight. He developed Stage 2 NEC at 14 days of age after tolerating full enteral feeds for four days. He received formula milk exclusively increasing at an average rate of 23ml/kg/day to achieve full feeds. His NEC was diagnosed based on radiological findings and was managed conservatively.

The z-score for weight for gestational age in 79 infants; and head circumference for gestational age in 60 infants changed by  $-0.7 \pm 0.8$  and  $0.1 \pm 1.8$  from birth to discharge. There were nine (11%) cases of LOS including four (5%) with positive blood or CSF cultures.

**A priori analyses**

*Gestation*

Higher gestational age at birth was associated with infants receiving the first (p<0.001), total (p<0.001), and full feeds earlier (p<0.001), as well as shorter hospital stay (p<0.001). (Figure 1).

*Total enteral feeding within 24 hours after birth*

Eleven (14%) infants achieved total enteral feeds within 24 hours after birth. They were of higher gestation compared to those who were not totally enteral fed by 24 hours (33 vs 32 weeks, p=0.004). They also achieved full feeds earlier (5 vs 8 days, p=0.02) and had shorter admissions (18 vs 30 days, p=0.009).

**DISCUSSION**

Two randomised trials (3, 4) have suggested that it is possible to achieve total enteral feeds from birth in 30–33 weeks preterm infants. However, these reports, with very small numbers, are from India where the healthcare setting is very different and the preterm population may not be representative of that in the UK. However, the risk of NEC is very low in infants above 30 weeks gestation and other emerging evidence supports early progressive feeding. (1, 2) Despite this, we found that only half of our consecutive sample of 80 infants from 8 UK neonatal units received their first feed by day 1 and total enteral feeds without any intravenous nutrition by day 5. Ninety percent of the cohort received their first feed by 55 hours and achieved total enteral feeds by 13 days of age.

Non-availability of breastmilk was reported to cause delay in starting feeds in half of the infants, raising the question of whether alternative milks such as donor breastmilk or formula milk should be utilised in this period or whether it is better to wait for maternal breastmilk. Studies to date are inconclusive and heterogeneity among the studies makes the evidence difficult to assess. (5)

Our study found that infants who were totally enteral fed within 24 hours after birth achieved full feeds earlier with shorter hospital stays without statistical differences in death, NEC or LOS.

However, our study was limited by a small sample size and the results were likely to be confounded by gestational age. This was because infants who were totally enterally fed within 24 hours after birth were also of higher gestational age. Mature infants were more likely to be given total enteral feeding, tolerate milk feeds, and be discharged sooner with lower risk of complications.

Hence, an adequately powered pragmatic randomised controlled trial is needed to assess whether providing total enteral feeding from birth in 30–33 weeks preterm infants improves outcomes and reduces hospital stay without increasing the risk of NEC in the UK. The trial would require a clear pathway to obtain parental consent and to allow deviation from study protocol for medical needs.

The trial is needed to re-evaluate current enteral feeding practices and enhance understanding of

enteral feeding physiology in moderate preterm infants which may differ from early preterm infants. This is crucial as total enteral feeding from birth may also be beneficial in resource rich settings like the UK. It may prevent unnecessary use of intravenous nutrition and venous access which are associated with infection and metabolic complications. It may also improve maternal-infant bonding experience by reducing the time of maternal-infant separation through earlier establishment of enteral feeding and earlier discharge.

**CONCLUSION**

Our study found that the feeding approach in 30–33 weeks preterm infants in the UK to be conservative. Total enteral feeding from birth is potentially feasible in these infants but further trials are needed before a change in practice can be recommended.

**ACKNOWLEDGMENTS**

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**COMPETING INTEREST**

None declared.

**FUNDING**

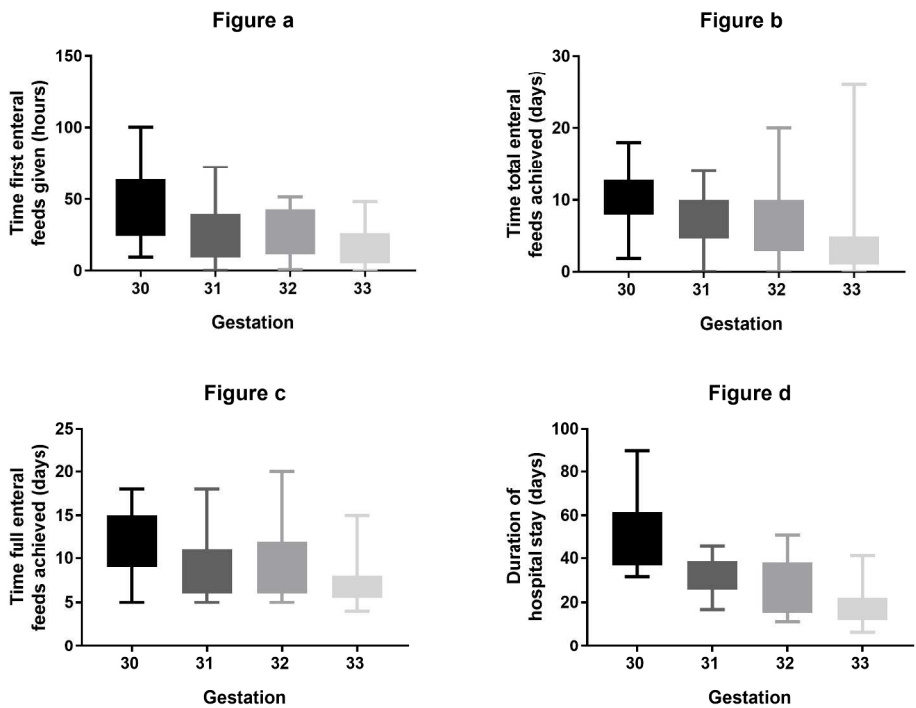
None declared.

**Figure 1: Box and whisker plots depicting the time first enteral feed (a), time total enteral feeds achieved (b) time full enteral feeds achieved (c) and duration of hospital stay (d) in infants at 30-33 completed weeks of gestation at birth.**

The box represents the interquartile range, while the whiskers represent the minimum and maximum values.

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