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Optimal gestational age at delivery for congenital diaphragmatic hernia

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Short title: When to deliver fetuses with diaphragmatic hernia?

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Key words: Congenital diaphragmatic hernia; survival; gestational age at delivery; prognosis; moderate forms; respiratory morbidity

Contribution

What are the novel findings of this work?

In comparison with delivery above 39 WG, delivery between 37^{+0} and 39^{+0} WG is associated with a higher survival rate at 28 days of life for moderate forms of CDH, independently of intrathoracic liver, management center, and mode of delivery.

What are the clinical implications of this work?

In fetuses with isolated left-sided CDH and moderate lung hypoplasia, delivery between 38^{+0} and 39^{+0} WG may be considered.

Abstract

Objectives To evaluate the neonatal morbidity and mortality of babies with isolated congenital diaphragmatic hernia (CDH) according to gestational age at delivery.

Methods We conducted a retrospective study in the University Hospitals of Antoine Béclère-Bicêtre and Leuven between January 1, 2010 and December 31, 2018. Isolated left-sided CDH cases were included. The Kaplan-Meier method was used to calculate cumulative survival at 28 days according to gestational age at delivery. The association between gestational age at delivery, as a continuous variable, and survival at 28 days was modeled using a fractional polynomial. Adjustment for position of the liver, management center, and mode of delivery was performed. The association was studied according to the severity of the CDH, defined by the o/e LHR, categorized in three classes: below 25%, between 25 and 45%, above 45%.

Results We included 213 fetuses with isolated left-sided CDH, with a median gestational age at delivery of 38^{+2} WG [IQR: 37^{+0}-39^{+6}]. Survival rates at 28 days and 6 months were 66.7% (142/213) and 64.3% (137/213), respectively. Kaplan-Meier curves showed higher survival up to 28 days for babies born between 37^{+0} and 39^{+0} WG than for those born after 39^{+0} WG (log-rank test, p<.001). In the subgroup of moderate forms, the survival rates at 28 days and 6 months were significantly higher for newborns delivered between 37^{+0} and 39^{+0} WG, compared to newborns delivered after 39^{+0} WG: 81.5% vs 61.5% (p=0.03). In this subgroup, 28-day survival significantly increased with advancing gestational age at birth until 38-39 WG (p=0.005) and significantly decreased from 39 WG.

Conclusions Delivery between 37^{+0} and 39^{+0} WG is associated with a higher survival rate at 28 days of life for moderate forms independently of intrathoracic liver, management center, and mode of delivery.

Introduction

Congenital diaphragmatic hernia (CDH) is a congenital birth defect that occurs in 0.8 per 5000 births when isolated [1,2]. Persistent pulmonary hypertension of the newborn and the degree of pulmonary hypoplasia are the main short-term prognostic determinants [3]. Preterm delivery in CDH babies is clearly associated with poor outcome [4–6], with survival rates ranging from 35% to 43% for babies delivered before 37^{+0} weeks of gestation (WG). This is particularly relevant in patients undergoing fetoscopic treatment with intratracheal balloon occlusion, as such therapy is associated with an increased preterm delivery rate [7].

Less information is available in the literature regarding the effect of gestational age on the outcomes of infants born after 37 weeks. In current clinical practice, induction of labor or elective cesarean section is usually performed to guarantee optimal pediatric expertise for the immediate neonatal management of newborns. Two studies have reported better outcomes for deliveries at 37-39WG when compared to 39-42WG [8,9], but did not consider antenatal prognostic factors for adjustment. Therefore, the question of the optimal gestational age at delivery has not been completely answered. The aim of this study was to evaluate the neonatal morbidity and mortality of babies with isolated left-sided CDH according to gestational age at delivery.

Materials and methods

This is a retrospective study on all fetuses in whom a diagnosis of isolated left-sided CDH was made in the prenatal period, who were followed up prospectively and were born between January 1, 2010 and December 31, 2018 at the university hospitals of Leuven in Belgium and Antoine Béclère/Bicêtre in France. Cases of isolated left-sided CDH, defined as the absence associated malformation or genetic abnormalities (either by karyotyping or CGH array without genomic imbalance), were included. Were excluded those fetuses who died in utero and pregnancies in which a termination was performed. Fetuses undergoing fetal tracheal occlusion were also excluded. Fetuses included in the TOTAL trial have not been included in this study. The postnatal management protocol was comparable at the two centers, which adhere to the Euro-CDH consortium protocol [10].

Data collection

The following data were collected: the observed/expected lung-to-head ratio (o/e LHR) and the presence or absence of intrathoracic liver herniation at ultrasound examination between 22 and 28 WG. The LHR was calculated as the ratio between the area of the lung contralateral to the lesion measured on a 4-chamber view and the head circumference [11]. The LHR was corrected for gestational age by using the formula developed by Peralta et al [12]. The following variables from the neonatal period were collected: gestational age at delivery, onset of labor (spontaneous, induction of labor or planned cesarean section), mode of delivery and birth weight.

Statistics

Descriptive results are presented as means with 95% confidence intervals or medians with interquartile range and percentages. Simple comparisons were made by using the $\chi 2$ Fisher exact (two-tailed) test for qualitative variables and Student's t-test for quantitative variables. Kaplan-Meier analysis was used to calculate cumulative survival at 28 days according to subgroups of the gestational age at delivery.

The association between gestational age at delivery, as a continuous variable, and survival at 28 days was modeled using a fractional polynomial. Adjustment for position of the liver, management center, and mode of delivery was performed. The association between survival and gestational age at birth was studied according to the severity of CDH, defined by the o/e LHR, categorized in three classes: below 25% (severe form), between 25 and 45% (moderate form), above 45% (good form). The statistical analyses were performed with Stata (StataCorp. Stata Statistical Software: Release 14. College Station; 2015).

This study received the approval of the Institutional Review Board (Comité de Protection des Personnes Ile de France VII: no 14-044).

Results

We identified 213 fetuses with isolated left-sided CDH assessed in the University Hospitals of Antoine Béclère-Bicêtre (n=126) and Leuven (n=87) during the study period. The population characteristics are summarized in Table 1. The median gestational age at delivery was 38^{+2} WG [37^{+0}-39^{+6}]. The preterm delivery rate was 20.2% (43/213). The rate of vaginal delivery was 76.7% (140/210), with a labor induction rate of 49% (n=101/206). Survival rates at 28 days and 180 days were 66.7% (142/213) and 64.3% (137/213), respectively. The survival rate at 28 days did not differ according to the mode of delivery, though there was a trend toward lower survival in the case of cesarean section: 58.6% (n=41/70) for cesarean section versus 71.4% (n=100/140) for vaginal delivery (p=0.06). In the subgroup of planned cesarean section, the survival rate was similar to the survival rate in the vaginal delivery group: 70.8% (17/24) (p=0.95). However, in the subgroup of emergency cesarean section, the survival rate was lower than the survival rate in the vaginal delivery group: 52.2% (24/46) (p=0.02).

The Kaplan-Meier curves of survival until 28 days according to gestational age at birth are displayed in Figure 1. Survival until 28 days was significantly higher in neonates born after 37^{+0} WG than in those born before 37^{+0} WG (log-rank test, p<.001) (Figure 1a). There was a trend towards higher survival up to 28 days for babies born between 37^{+0} and 39^{+0} WG than those born after 39^{+0} WG (log-rank test, p<.001) (Figure 1b).

Table 2 shows the comparison in outcomes between newborns delivered between 37^{+0} and 39^{+0} WG and those delivered after 39^{+0} WG, in the subgroup of moderate CDH forms. In those delivered after 39^{+0}WG, there was a trend toward more advanced ventilatory/oxygenation modalities (more ECMO, more inhaled nitric oxide, more pulmonary hypertension), but this was not significant (Table 2). The survival rate at 28 days was significantly higher for newborns delivered between 37^{+0} and 39^{+0} WG, compared to newborns delivered after 39^{+0} WG: 81.5% vs 61.5% (p=0.03). Survival at 6 months was significantly higher for neonates with a moderate CDH form delivered between 37^{+0} and 39^{+0} WG (p=0.01). The association between survival rate at 28 days adjusted for the risk factors liver position, o/e LHR, management center, and mode of delivery is displayed in Figure 2.

In the entire study population, there was a significant association between survival rate and gestational age at birth (Figure 2a). In fetuses with an o/e LHR between 25 and 45%, 28-day survival significantly increased with advancing gestational age at birth until the approximate gestational age of 38-39 WG (Figure 2c) (p=0.005) and significantly decreased from 39 WG on (p=0.005). There was no such association between gestational age at delivery and survival at 28 days in cases with o/e LHR <25% or >45% (Figures 2b and 2d) (p=0.11 and p=0.97, respectively).

Discussion

In these cohorts, preterm delivery before 37^{+0} WG was strongly associated with a lower survival rate. Delivery between 37^{+0} and 39^{+0} WG was associated with a higher survival rate at 28 days of life for moderate forms, independently of intrathoracic liver, management center, and mode of delivery.

Interpretation of the literature

In line with previous studies [6,13], we show that preterm delivery is associated with an increased mortality rate. This result is particularly important in the context of fetoscopic treatment, which could increase the risks of premature rupture of membranes and of preterm delivery [5].

We also found that for moderate CDH forms, the late term deliveries (after 39^{+0} WG) are associated with a lower survival rate both at 28 days and 6 months when compared to near-term deliveries (between 37^{+0} and 39^{+0}WG), which is consistent with one previous study [14]. Safavi et al compared outcomes in 209 newborns, categorized as preterm delivery (before 37^{+0} WG); early term (37^{+0}-38^{+0} WG); late term (after 39^{+0} WG) [14]. They showed a trend towards higher survival at discharge for early term newborns (86%) compared to preterm (77%) and late term (79%) newborns, although the difference was not significant. However, non-isolated forms of CDH and postnatally detected cases were included in that study. Another study comparing pediatric outcomes, especially neurodevelopmental, according to gestational age at birth in four

classes did not show better outcomes for full-term deliveries (39-41 WG) than in the near-term (37-38 WG) in CDH survivors [5].

Jani et al found that pulmonary hypertension is more frequent as the gestational age at delivery is advanced [15]. This could explain worse respiratory morbidity especially pulmonary hypertension above 39 WG, as observed in our seria.

A recent randomized trial compared outcomes after systematic induction of labor at 39^{+0} WG to expectant management until 41^{+0} WG in low-risk nulliparous women with normal fetuses [16]. There was a significantly higher need for respiratory support in the expectant management group than in the induction at 39^{+0} WG group[16]. This could suggest that a physiological term of the pregnancy could be earlier than 42^{+0}WG. In newborns with CDH, a worse outcome could be explained by the progressive nature of pulmonary hypoplasia [17] or a change in vasoreactivity with increasing gestational age [17].

In practice, our results suggest that the delivery should be planned between 38^{+0} and 39^{+0}WG.

As previous studies have shown, the mode of delivery (i.e. vaginal delivery or cesarean section) was not associated with either neonatal morbidity or mortality [14,18]. In our study, the vaginal delivery rate was around 73%, with an attempt at vaginal delivery in 87% of cases. The survival rate was comparable between planned cesarean delivery and vaginal delivery, but lower in the subgroup of emergency cesarean than in the vaginal delivery group. The mode of delivery should depend on the obstetrical

indications and CDH is not a sufficient reason on its own to plan a cesarean section. However, the impact of emergency cesarean section on outcome should be further investigated. The time of delivery (day or night) is also an important factor to consider, in terms of the availability of neonatologists. However, some authors have shown that the time of delivery is not associated with morbidity or the survival of neonates with CDH [14,18]. We did not evaluate this parameter in our study, because pediatricians were available day and night in the two centers.

Strengths

Our study is the first to assess the relationship between gestational age at delivery as a continuous variable and independently of antenatal prognostic factors, mode of delivery, and survival rate. Unlike previous studies, only left-sided forms of CDH were included and the associated forms of CDH were excluded to have a homogeneous population. Previous studies have considered gestational age at birth as a categorical variable [5,14].

Limitations

The retrospective design of the study is a limitation, however, all data were collected prospectively. This was also a two-center study, though both centers use the same standardized European neonatal management protocol [19] and similar standardized prenatal assessment methods [20]. To avoid confounders, we did not include fetuses who underwent fetoscopic tracheal occlusion, as the procedure itself might have an impact on postnatal survival.

Furthermore, the association between gestational age at delivery and survival was only found for babies previously diagnosed with moderate lung hypoplasia. In our study, this moderate form group is the largest compared to severe and good prognostic forms. The low number of severe and good forms could also explain the lack of strength. Other studies are therefore needed to investigate the effect of gestational age at birth in fetuses undergoing fetal therapy. The other forms, like right or bilateral CDH, or associated structural or genetic anomalies have a different prognosis [21].

Perspectives

Larger studies are needed to assess the optimal gestational age at delivery. Studies are also necessary to understand the physiological modifications at term.

Conclusion

In fetuses with isolated left-sided CDH and moderate lung hypoplasia, near-term delivery is associated with an improved survival rate. Given the similar survival rates in induced and spontaneous labor, one may therefore consider induction of labor between 38 and 39 WG in isolated CDH.

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Conflict of Interest

The authors have no conflict of interest to declare.

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Figure legends

Figure 1. Kaplan-Meier curve of survival until 28 days according to gestational age at birth
a. in two classes: before 37+0 WG and after 37+0 WG (Log rank test, p<0.001)
b. in four classes: before 34+0 WG, between 34+0 and 37+0 WG, between 37+0 and 38+6 WG and after 39+0 WG (Log rank test, p<0.001)

Figure 2. Survival rate at 28 days according to gestational age at delivery
Modeling using a fractional polynomial. Adjustment for liver position, management center, and mode of delivery.
a. In the entire study population. Adjustment for liver position, management center, mode of delivery, and o/e LHR.
b. Severe forms (o/e LHR <25%), n= 35 (p=0.11)
c. Moderate forms (o/e LHR between 25 and 45%), n=128 (p=0.005)
d. Good forms (o/e LHR >45%), n=50 (p=0.97)

Tables

Table 1. General characteristics, isolated left-sided congenital diaphragmatic hernia (n=213)

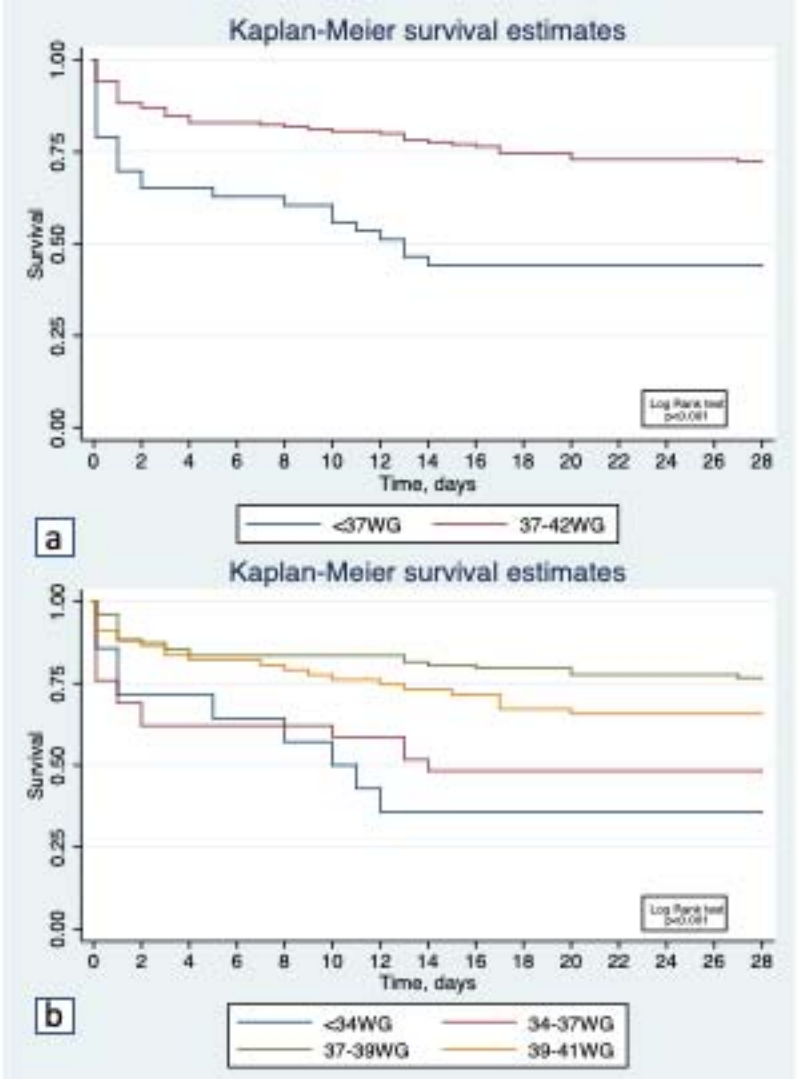
Antenatal characteristics	
o/e LHR	34.0% [27.0-43]
Severe forms o/e LHR below 25%	16.4% (35)
Moderate forms o/e LHR between 25 and 45%	60.1% (128)
Good forms: o/e LHR above 45%	23.5% (50)
Intra-abdominal liver	59.6% (127/213)
Delivery	
Induction of labor	
Spontaneous labor	39.3% (81/206)
Induction of labor	49.0% (101/206)
Planned cesarean section	11.7% (24/206)
Gestational age at delivery	38^{+2} [37^{+0} -39^{+1}]
Attempt of labor	86.3% (182/211)
Cesarean section	33.3% (70/210)
Neonatal morbidity	
Duration of ventilation (days)	13.0 [4-24]
Pulmonary hypertension in first 5 days	60.1% (133)
Inhaled nitric oxide ventilation	65.4% (100/153)
ECMO	15.3% (30/196)
Survival	
Survival at 28 days	66.7% (142/213)
Survival at 6 months	64.3% (137/213)
Surgical characteristics	
Surgery	78.8% (167/212)
Age at surgery	2.0 days [1.0-3.7]
Patch repair	60.9% (98/161)

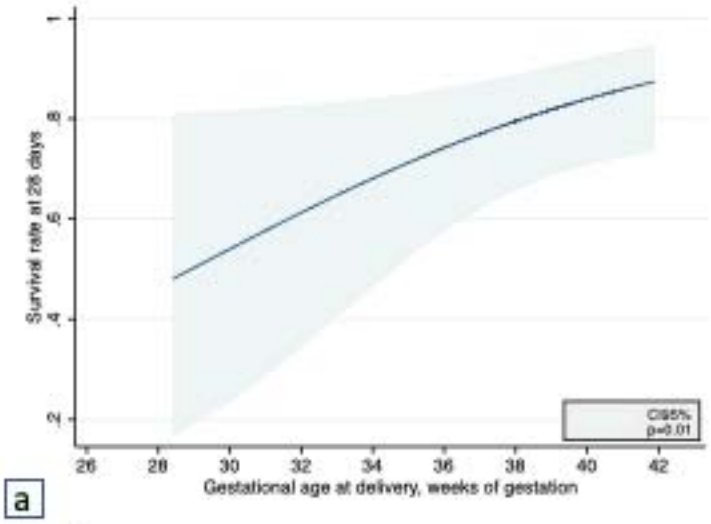
Data are expressed as medians with their interquartile range or percentages (n).

Table 2. Comparison according to gestational age at delivery at term: early (between 37^{+0}-39^{+0} weeks of gestation [WG]) versus late (after 39^{+0} WG) gestational age at birth for fetuses with moderate CDH forms (o/e LHR between 25% and 45%)

Antenatal characteristics	**Birth between 37-39 Weeks of gestation n= 65**	**Birth between 39-42 Weeks of gestation n=34**	**p**
o/e LHR	34.0% [29.9-38.9]	34.0% [27.7-40.0]	0.87
Intra-abdominal liver	69.2% (45/65)	58.8% (20/34)	0.37
Delivery			
Gestational age at delivery	38^{+0} [37^{+6}-38^{+3}]	39^{+4} [39^{+1}-40^{+2}]	<0.001
Birth weight	3100g [2805-3320]	3235g [2938-3407]	0.24
Umbilical artery pH below 7.15	9.1% (2/22)	4.2% (1/24)	0.97
Cord blood lactates > 6mmol/L	11.8% (2/17)	11.1 (2/18)	0.95
Neonatal morbidity			
Duration of ventilation (days)	16 [7-29]	17 [9-31]	0.64
Pulmonary hypertension at 48 hours of life	62.9% (22/35)	80.0% (20/25)	0.15
Inhaled nitric oxide ventilation	65.8% (27/41)	85.2% (23/27)	0.10
Extracorporeal Membrane Oxygenation	18.0% (11/61)	26.5% (9/34)	0.33
Survival			
Survival at 28 days	81.5% (53/65)	61.8% (21/34)	0.03
Survival at 6 months	80.0% (52/65)	55.9% (19/34)	0.01
Surgical characteristics			
Surgery	86.1% (56)	82.3% (28)	0.77
Age at surgery, days	2 [2-5]	2 [1-3]	0.38
Patch repair	63.5% (33/52)	70.4% (19/27)	0.54

Data are expressed as medians with their interquartile range or percentages (n). Qualitative data are compared with Chi2 and quantitative data are compared with Student's t-test.





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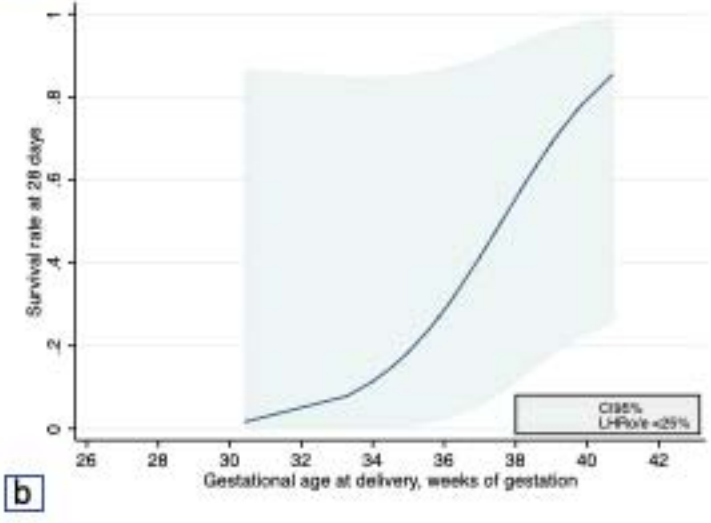

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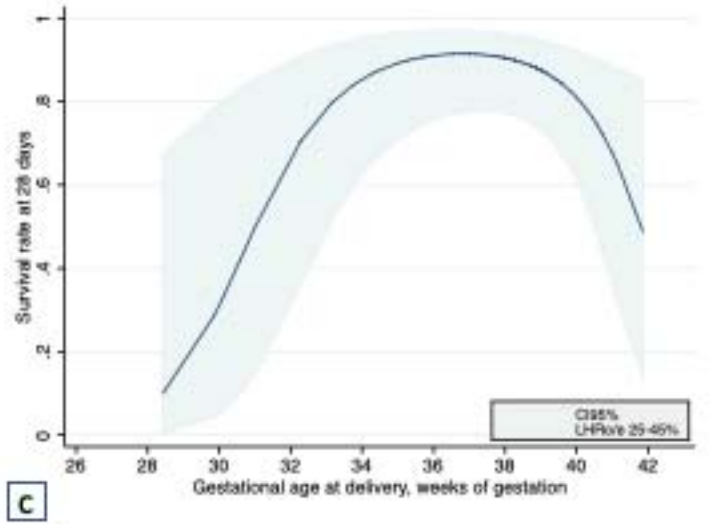

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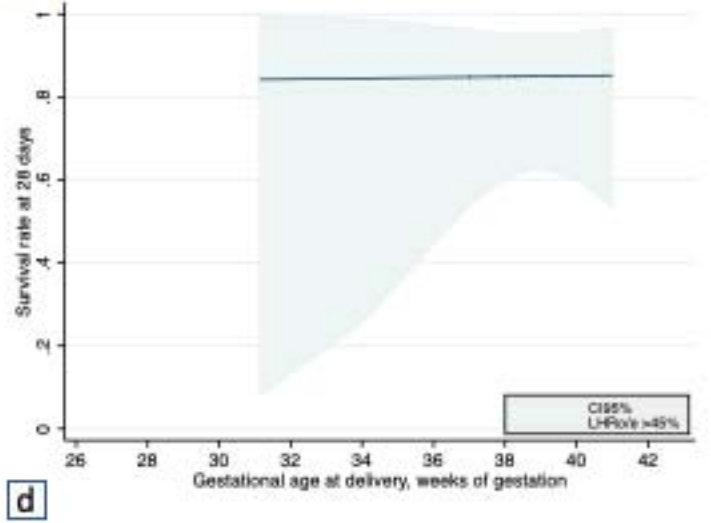

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