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Cerebral palsy among term and post-term births

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Abstract

Context—While preterm delivery is a well-established risk factor for cerebral palsy (CP), preterm deliveries contribute only a minority of affected infants. There is little information on the relation of CP risk to gestational age in the term range, where most CP occurs.

Objective—To determine whether timing of birth in the term and post-term period is associated with risk of CP.

Design, Setting, and Participants—Population-based follow-up study using the Medical Birth Registry of Norway to identify 1,682,441 singleton children born 1967-2001 with a gestational age of 37-44 weeks and no congenital anomalies. The cohort was followed through 2005 by linkage to other national registries.

Main Outcome Measures—Absolute and relative risk of CP for children surviving at least to 4 years of age.

Results—Of the cohort of term and post-term children, 1,938 were registered with CP in the National Insurance Scheme. Infants born at 40 weeks had the lowest risk of CP, with a prevalence of 0.99 per thousand (95% confidence interval [CI], 0.90-1.08). Risk for CP was higher with earlier or later delivery, with relative risk reaching 1.9 at 37 weeks (95% CI, 1.6-2.3) and 1.4 at 42 weeks (95% CI, 1.2-1.6). These associations were even stronger in a subset with gestational age

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based on ultrasound measurements – at 37 weeks the risk was 3.7 (95% CI, 1.5-9.1), and at 42 weeks 2.4 (95% CI, 1.1-5.3). Adjustment for infant sex, maternal age and various socioeconomic measures had little effect.

Conclusions—Compared with delivery at 40 weeks gestation, delivery at 37 weeks or at 42 weeks was associated with an increased risk of CP

Introduction

Cerebral palsy (CP) is the most common cause of physical disability in childhood, with limitations that persist throughout life.¹⁻³ Cerebral palsy is characterized by non-progressive disorders of movement and posture, presumed to result from insult to the brain during fetal or early infant life.⁴ These motor problems are often accompanied by disturbances of cognition and other neurologic difficulties.^{1, 3, 4} Cerebral palsy can be a severe handicap and a substantial burden for the family and society.

The underlying causes of CP remain largely unknown.⁵ Cerebral palsy is associated with difficult labor and delivery, but most cases have little apparent association with delivery care.^{6, 7} One of the strongest predictors of CP is preterm birth, with the risk of CP rising steadily with earlier delivery.⁸ While risk is much less among term births, about three-fourths of all infants with CP are born after 36 weeks.⁸ Within this range of term births, there are few data on the possible association of CP with gestational age. We explored the relation of CP risk with gestational age among term and post-term births, using national health and insurance registries in Norway.

Methods

Study cohort

Each Norwegian citizen has a unique identification number that allows linkage of a person's data among the national registries. The Medical Birth Registry of Norway has collected information since 1967 on all births with a gestational age of at least 16 weeks.⁹ Information on gestational age is based on the last menstrual period (LMP). Using the birth registry, we identified all singleton live births from 1967 through 2001 with a gestational age of 37 to 44 weeks. Follow-up data were available through 2005. In order to remove likely errors of gestational age based on LMP, we excluded infants with birth weights more than 3 standard deviations from the mean for a given gestational-age week, stratified by infant sex.¹⁰ Birth defects are associated with CP and also with gestational age at birth.¹¹ In order to help remove possible confounding by birth defects, we also excluded infants with any registered congenital anomalies. (Birth defects were coded using International Classification of Diseases (ICD), version 8 and 10 in the Medical Birth Registry, and version 9 and 10 in the insurance registry.¹²)

Cerebral palsy cannot be diagnosed at birth. Our data on CP came from the Norwegian compulsory health insurance system.¹³ Persons with disabilities in Norway are entitled to benefits for disability that involves significant expenses, requires special attention or nursing, or reduces working capacity by at least 50 per cent.¹⁴ These benefits are provided without regard to income or wealth, and are considered to provide a fairly complete registry of disabled persons in Norway.

Benefits are based on physician diagnosis, with diagnoses registered according to ICD 9 or 10. We obtained information on CP (ICD-9: 342-344, ICD-10: G80-G83) using the medical diagnoses linked to the disability benefits defined above. A validation study has shown that

registered CP diagnoses correspond well with medical records, with some under-registration of the mildest cases.¹⁵

There is controversy regarding the youngest age at which CP can be reliably diagnosed.^{16, 17} Most cases are established by age four, and so we required our cohort to survive and be followed to at least the age of four. Information on deaths was obtained through the Cause of Death Registry. Information on parents' education and immigration status came from the Norwegian National Education Database and Statistics Norway.¹⁸

The study was approved by The Norwegian Data Inspectorate, The Norwegian Labor and Welfare Organization, The Office of the National Registrar and The Norwegian Directorate of Health. These institutions gave permission to use the data in an anonymous form without requiring consent by study participants.

Statistical analyses

We first estimated the prevalence of CP according to gestational day of birth for all births from 37 to 44 weeks. In further analyses, we categorized gestational age into seven groups: 37 weeks (i.e. 259 to 265 days), 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, and 43-44 weeks. The ratios of the estimated prevalence rates have been expressed as relative risks, with 40 weeks as the reference. We estimated the relative risk of CP for each gestational group using log-binomial regression, and adjusted for year of birth, sex, maternal age, single motherhood, mother's level of education, father's level of education, and immigrant status of the parents.

Since at least 1994, an estimated 98 % of pregnant women in Norway have received a routine ultrasound examination by the mid-second trimester.¹⁹ These data have been reported in the Medical Birth Registry starting in December 1998. We explored the quality of LMP data by repeating the overall analysis using ultrasound measures of gestational age for the subset of infants born since December 1998.

Year of birth, mother's level of education and father's level of education were entered as continuous variables; the remaining were categorical. Maternal age was in three categories (less than 18 years, 18 through 39 years and above 39 years). Father's and mother's education was defined on a 9-level scale, with 0 for no education and 8 (the highest) for a doctoral degree. A child was considered to have immigrant parents if both parents were born outside Norway. Since the members of the study cohort were born across a 35-year time span, we repeated the analyses in three smaller time windows (1967-1977, 1978-1989, and 1990-2001).

SPSS Statistics 17.0 was used for statistical analyses. All tests were 2-sided with 5 % significance level. Graphs were made by Sigmaplot 9.0, including a LOESS-smoothed curve of prevalence of CP per day.

Results

There were 2,024,215 live births in Norway from 1967 through 2001. We excluded those missing data on gestational age (6.0%), those born preterm (5.5%), those with gestational age more than 44 weeks (1.0%), those whose birth weights were incompatible with their gestational age (0.7%), twins or other multiple births (1.3%), those with malformations recorded either in the birth registry or the insurance registry (2.0%) and those who died before 4 years of age (0.4%). This left an analysis cohort of 1,682,441 singleton births with a gestational age of at least 37 weeks.

Figure 1 shows the distribution of these births by gestational day at delivery, with a summary smoothed curve. There were 1,938 persons subsequently registered with CP (1.15 per 1000 births; 95% CI, 1.10-1.20). Delivery at 40 weeks was associated with lowest CP risk. Compared with the risk at 40 weeks, CP risk was 1.9 (95% CI, 1.6-2.4) at 37 weeks and 1.4 (95% CI, 1.2-1.6) at 42 weeks (Figure 2).

The Table shows characteristics of the parents, infants, and deliveries for children with and without subsequent CP. Children with CP were slightly more likely to have single mothers ($P=.03$), and parents with less education ($P<.001$). Complications of labor and delivery (breech, cesarean section) were up to twice as likely for infants who were later diagnosed with CP ($P<.001$). Boys were overrepresented among CP children ($P<.001$). Cerebral palsy children had lower mean birth weight (3437 gm vs. 3585 gm, $P<.001$) and smaller head circumference (35.1 cm vs. 35.3 cm, $P<.001$). Cerebral palsy children were 73 times more likely to have had an Apgar score below 4 ($P<.001$), and were 8 times more likely to have been transferred to a pediatric unit after delivery ($P<.001$). Most of these associations were present at each gestational age of delivery.

Adjustment for year of birth, infant sex, maternal age, presence or absence of a partner, educational level of the mother and father, and immigrant status of the parents had little effect on risk by gestational age. We plotted the association of gestational age with disabilities that were unlikely to be caused by time of delivery in order to explore the possibility of reverse causation or selection. Congenital malformations had a weak U-shaped association with gestational age, while diseases of the digestive system (for example) did not (Figure 2, supplementary data in eTable).

LMP is an error-prone measure of gestational age.²⁰ Ultrasound-based measurements of gestational age were available for the subset of 139,976 children born in December 1998 and later, including 85 with CP. Among this subgroup, the pattern of CP risk with gestational age was stronger with ultrasound-based gestational age than with LMP (see eFigure 1). Compared with infants born at 40 weeks, infants at 37 weeks had 3.7-fold higher risk of CP (95% CI, 1.5-9.1), while infants at 42 weeks had 2.4-fold higher risk (95% CI, 1.1-5.3), based on ultrasound dating of gestational age.

Changes in CP prevalence and gestational-age distribution over time might have affected our results. The prevalence of CP from 37 weeks onward decreased from 1.4 per 1000 (95% CI, 1.3-1.5) to 0.7 per 1000 (95% CI, 0.6-0.8) over the course of our study (eFigure 2). The association of CP with gestational age, however, was consistent over time (eFigure 3).

Comment

Much attention has been given to the high risk of CP with preterm delivery.²¹⁻²⁵ The risk of CP among term infants may be relatively low, but most children with CP are the product of term deliveries. Furthermore, the risk at term and beyond is not uniform. The risk of CP is lowest at 40 weeks, with the highest risks at 37 weeks and at 42 weeks or later. A recent report supports our finding of increased CP risk among postterm births.¹⁶ Other neurologic conditions have also been found to vary by gestational age at term. A U-shaped pattern for low IQ was recently reported among term and postterm births.²⁶

Our findings do not appear to be due to errors in LMP. The U-shaped risk was even stronger among the subgroup with ultrasound measures of gestational age (which are still imperfect, but with less error than LMP).²⁰ Such a strengthening of effect would be expected if the association with gestational age was true but blunted by measurement error related to LMP.

We had information on several parental and birth characteristics associated with a later diagnosis of CP. These risk factors are consistent with results from other studies.^{15, 27-31} The distribution of risk factors across 37-to-44 week births was generally similar for the CP and non-CP group (Table). Adjustment for parental characteristics had no influence on the results. We did not adjust for circumstances of labor, delivery or neonatal period because these may be part of the causal pathway, or an early expression of CP.

Causal interpretation

Cerebral palsy risk has a robust U-shaped association with gestational age among infants reaching term. The biological mechanisms that underlie this association are not as clear. One possible interpretation is that delivery too early or too late – even within the limited range of term and post-term births – increases the risk of CP. If so, clinical interventions at 37 or 38 weeks (through caesarean section or induction of labor) could increase the risk of CP. Conversely, obstetric intervention after 40 weeks might reduce CP risk.

However, an equally plausible interpretation is that fetuses predisposed to CP have a disturbance in the timing of their delivery, which causes them to be more often delivered early or late. This apparently happens with other fetal conditions: there is a U-shaped pattern in the risk of congenital anomalies with gestational age after 37 weeks (Figure 2). Since congenital anomalies are not caused by the timing of delivery, the most plausible explanation is reverse causation: malformed infants experience disruptions in their time of delivery, with increased chance of delivery either earlier or later than 40 weeks.

While the forces that regulate timing of a normal delivery are poorly understood,^{32, 33} it appears that the malformations most likely to disrupt the timing of delivery often involve cerebral function. For example, anencephalic fetuses have a tendency to be born postterm,^{34, 35} children with Trisomy 18 to be born preterm or postterm,³⁶ and children with Down syndrome to be born early.³⁷ It is possible that the cerebral damage later expressed as CP has similar disruptive effects.

The question of causal interpretation has been a long-standing puzzle for CP in another important respect. Labor and delivery complications are commonly found in infants subsequently diagnosed with CP (Table). This could indicate that CP is caused by damage to the infant in the course of delivery, but it could also mean that the prenatal factors leading to CP cause problems of delivery.^{16, 38} The lower birth weight and head circumference at birth among CP cases suggest that these children differ from non-CP infants even before birth. As with most previous studies, our study has no possibility of discerning prenatal from perinatal or postnatal causes of CP.

Strengths and weaknesses

A strength of this study is its population-based cohort design. This provides statistical power for gestational-age specific estimates of risk during the term and postterm periods, when risk of CP is low. The study design also avoids problems of selective participation, detection bias, recall bias, and loss to follow up.

We were able to adjust for possible risk factors including maternal age, single motherhood, mother's and father's level of education, and immigrant status of the parents and infant sex. These factors made little difference to the results.

One notable weakness of the study is the lack of any information on subtypes of CP. We are unable to determine, for example, whether the risks with gestational age are more pronounced for certain subtypes. Furthermore, by using a disability register to identify CP, we may lose information of some of the mildest CP cases, as suggested by an earlier

validation study.¹⁵ The CP cases in the present study may in general be more severe than if they had been identified by hospital or clinic records.

The exclusion of children who died before four years of age could potentially bias the results by excluding the most severe cases of CP. Of the 7096 children who died before four years of age, only 3 had a diagnosis of CP. Repeated analyses after inclusion of all children who died before the age of four had no effect on the results.

Another possible difficulty is the accumulation of births over a long time interval (35 years). Changes in obstetric practice, CP diagnosis, and the recording of gestational age or other study variables may have affected the results. However, when stratifying by time period, there was no evidence that the association of gestational age with CP differed over time (eFigure 3).

Neonatal mortality fell by 75% during the study period. Some children who survived with CP in more recent years might have died if they had been born in earlier years, which could lead to an increase in severe cases of CP over time. What we observe, however, is the opposite: the prevalence of CP has declined slightly over time (eFigure 2). Factors that have reduced neonatal mortality may also have reduced the risk of CP.

Clinical implications

Clinicians typically regard term births (37 to 41 weeks¹⁴) as “low risk,” with the possibility of increased risk with post-term delivery.³⁹ As seen in Figure 1, this standard definition of “term” does not correspond well with the period of lowest risk for CP, or with the weeks when most infants are born. Weeks 37 and 38 seem more to resemble weeks 42 and 43, both in CP risk and in the general likelihood of delivery, leaving 39-41-weeks as the optimum time for delivery.

Given these patterns, it is not possible to determine whether the time of delivery affects CP risk (providing an opportunity for constructive intervention), or alternatively whether infants prone to CP are disrupted in their delivery times. To the degree the latter is true, then the prevalence of CP would be unchanged even if all infants were delivered at 40 weeks. A definitive answer would require a randomized clinical trial of deliveries at various gestational ages – an impractical option, given the very low prevalence of CP. For those inclined toward the former interpretation, the increased CP risk at 37 or 38 weeks would suggest that elective delivery at this time is not as benign as usually assumed. However, a non-causal U-shaped risk is present with congenital anomalies, and may occur with other fetal conditions. If such mechanisms are at work for CP, then a change in time of delivery would have no influence on a child's underlying risk of CP. Until the underlying reasons for these patterns of risk in term and post-term births are better understood, it would be hasty to assume that interventions on gestational age at delivery could reduce the occurrence of CP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Daily prevalence of cerebral palsy per 1000 (top panel) and daily number of births (lower panel) according to gestational age at birth from 37 weeks to 44 weeks among the 1,682,441 members of the study cohort. The smoothed curve (top panel) was fitted using the LOESS method.

Figure 2.

Information on CP and digestive diseases (ICD-9: 520-579, ICD-10: K00-K93) is from the study cohort of 1,682,441 members, whereas information on congenital anomalies is based on 1,720,443 persons (original study cohort, without exclusion of congenital anomalies). Error bars indicate 95% confidence intervals.

Table

Characteristics of the CP and non-CP cases stratified by gestational age at birth.

	Total	37 weeks	38 weeks	39 weeks	40 weeks	41 weeks	42 weeks	43 weeks ^a
Total number	1,938 1,680,503 1.15	123 64,160 1.91 1.9 (1.6-2.3)	193 154,435 1.25 1.3 (1.1-1.5)	376 341,035 1.10 1.1 (1.0-1.3)	486 488,999 0.99 1.0 (ref)	417 384,037 1.08 1.1 (1.0-1.2)	248 181,757 1.36 1.4 (1.2-1.6)	95 66,080 1.44 1.4 (1.2-1.8)
Maternal age at birth <18 yr - % (n) 40 yr - % (n)	With CP Without CP CP per 1000 Crude RR (95% CI)	0.8 (1) 1.6 (1,035) 0.8 (1) 2.2 (1,384)	1.0 (2) 1.3 (1,943) 1.0 (2) 2.1 (3,296)	1.6 (6) 1.1 (3,663) 3.7 (14) 1.7 (5,733)	1.4 (7) 1.1 (5,487) 1.2 (6) 1.3 (6,574)	1.7 (7) 1.2 (4,547) 1.2 (5) 1.1 (4,308)	2.0 (5) 1.4 (2,598) 0.0 (0) 0.9 (1,654)	0.0 (0) 1.8 (1,185) 2.1 (2) 0.9 (584)
Single mother - % (n)	With CP Without CP	12.2 (15) 11.1 (7,107)	8.8 (17) 9.6 (14,863)	10.6 (40) 8.7 (29,572)	11.1 (54) 8.7 (42,634)	11.3 (47) 9.6 (36,738)	11.3 (28) 10.9 (19,750)	11.6 (11) 12.7 (8,390)
Level of mother's education, mean (SD) ^b	With CP Without CP	3.6 (1.5) 3.9 (1.6) P<.001	3.6 (1.6) 3.8 (1.6)	3.5 (1.5) 3.8 (1.6)	3.5 (1.5) 3.9 (1.6)	3.5 (1.5) 3.9 (1.6)	3.7 (1.5) 3.8 (1.6)	3.6 (1.5) 3.7 (1.6)
Level of father's education, mean (SD) ^b	With CP Without CP	3.8 (1.6) 4.0 (1.7) P<.001	4.0 (1.7) 4.0 (1.7)	3.7 (1.6) 4.0 (1.7)	3.7 (1.6) 4.0 (1.7)	3.8 (1.6) 4.0 (1.7)	3.8 (1.6) 4.0 (1.6)	3.8 (1.6) 3.8 (1.6)
Immigrant parents, % (n) ^c	With CP Without CP	1.5 (29) 2.4 (39,135) P=.02	1.1 (2) 3.7 (5,512)	1.4 (5) 2.9 (9,661)	1.9 (9) 2.2 (10,423)	1.7 (7) 1.8 (6,765)	1.3 (3) 1.7 (3,048)	1.1 (1) 2.0 (1,307)
Birth weight, mean (SD), g	With CP Without CP	3437 (556) 3585 (480) P<.001	3196 (493) 3328 (450)	3350 (516) 3488 (442)	3518 (531) 3617 (449)	3564 (518) 3711 (461)	3580 (542) 3751 (477)	3609 (490) 3695 (484)
Head circumference, mean (SD), cm	With CP Without CP	35.1 (1.7) 35.3 (1.5) P<.001	34.6 (1.5) 34.8 (1.5)	34.9 (1.6) 35.1 (1.4)	35.3 (1.7) 35.4 (1.4)	35.3 (1.6) 35.6 (1.4)	35.7 (1.8) 35.8 (1.4)	35.7 (1.8) 35.7 (1.5)
Male sex, % (n)	With CP Without CP	57.2 (1,109) 50.9 (856,004) P<.001	56.1 (69) 56.2 (36,036)	56.1 (211) 52.5 (178,978)	61.9 (301) 50.2 (245,571)	53.7 (224) 49.3 (189,291)	55.6 (138) 49.1 (89,247)	52.6 (50) 49.0 (32,399)
Cesarean section, % (n)	With CP Without CP	14.4 (279) 7.2 (120,793) P<.001	27.6 (34) 14.1 (9,054)	13.0 (49) 8.4 (28,793)	11.9 (58) 5.1 (24,781)	9.8 (41) 5.2 (20,081)	14.9 (37) 7.2 (13,097)	18.9 (18) 8.3 (5,459)
Forceps, % (n)	With CP Without CP	3.9 (76) 2.4 (39,773) P<.001	2.4 (3) 1.7 (1,091)	3.1 (6) 1.7 (2,644)	4.5 (22) 2.2 (10,964)	3.4 (14) 2.8 (10,708)	4.4 (11) 3.3 (6,031)	10.5 (10) 3.2 (2,126)

	Total	37 weeks	38 weeks	39 weeks	40 weeks	41 weeks	42 weeks	43 weeks ^a
Vacuum, % (n)	6.7 (130) 3.9 (65,923) P<.001	1.6(2) 2.7(1,727)	5.2 (10) 2.7 (4,150)	6.9 (26) 2.9 (9,967)	5.3 (26) 3.7 (18,019)	8.2 (34) 4.7 (18,102)	8.1 (20) 5.7 (10,306)	12.6 (12) 5.5 (3,652)
Breech or other malpresentations, % (n)	7.0 (135) 4.3 (72,940) P<.001	5.7 (7) 5.9 (3,801)	10.4 (20) 5.5 (8,423)	6.1 (23) 4.7 (15,961)	4.7 (23) 3.9 (19,229)	8.6 (36) 3.9 (15,160)	5.6 (14) 4.2 (7,574)	12.6 (12) 4.2 (2,792)
Inductions, % (n)	14.1 (273) 11.1 (186,181) P<.001	7.3 (9) 10.5 (6,710)	8.8 (17) 8.8 (13,575)	9.3 (35) 7.0 (23,915)	10.1 (49) 7.6 (37,362)	13.2 (55) 11.2 (43,004)	30.6 (76) 25.3 (45,980)	33.7 (32) 23.7 (15,365)
Apgar scores at 5 minutes ^d 0 through 3, % (n) 4 through 6, % (n)	7.1 (80) 0.1 (945) P<.001 12.0 (134) 0.5 (5,645) P<.001	3.5 (3) 0.2 (76) 14.1 (12) 0.9 (388)	8.8 (10) 0.1 (85) 8.8 (10) 0.5 (516)	5.3 (11) 0.1 (164) 10.2 (21) 0.4 (938)	7.7 (22) 0.1 (236) 9.4 (27) 0.4 (1,354)	9.6 (23) 0.1 (221) 13.8 (33) 0.5 (1,333)	6.4 (9) 0.1 (112) 15.6 (22) 0.6 (756)	4.2 (2) 0.1 (51) 18.8 (9) 0.9 (360)
Rupture of membranes 12 h before delivery, % (n) ^e	15.1 (14) 9.1 (13,390) P=.04	33.3 (8) 13.0 (2,784)		9.1 (1) 10.1 (2,961)	12.5 (2) 8.5 (3,490)	4.5 (1) 7.9 (2,582)	10.0 (2) 7.0 (1,573)	
Meconium stained amniotic fluid, % (n) ^e	31.2 (29) 17.4 (25,624) P<.001	25.0 (6) 7.0 (1,489)		36.4 (4) 11.4 (3,363)	18.8 (3) 17.3 (7,107)	36.4 (8) 23.2 (7,583)	40.0 (8) 27.2 (6,082)	
Prolonged labor, % (n) ^e	9.7 (9) 6.9 (10,175) P=.29	12.5 (3) 4.2 (908)		9.1 (1) 5.1 (1,489)	6.3 (1) 6.6 (2,717)	9.1 (2) 8.5 (2,770)	10.0 (2) 10.2 (2,291)	
Neonate transferred to pediatric service, % (n) ^e	41.9 (39) 5.3 (7,753) P<.001	37.5 (9) 8.7 (1,861)		27.3 (3) 4.6 (1,339)	37.5 (6) 4.2 (1,713)	40.9 (9) 4.7 (1,538)	60.0 (12) 5.8 (1,302)	

Abbreviations: CP, cerebral palsy; RR, relative risk; CI, confidence interval; yr, years; SD, standard deviation; h, hours.

^aThe category includes gestational age from 43 weeks and 0 days through 44 weeks and 6 days.

^bEducation level was assessed on a national scale from 0 to 8 where 0 resembles no education and 8 the highest degree at university level.

^cParents were considered immigrants if both parents were born abroad.

^dApgar score reliably recorded in MFR from 1978

^eInformation was available from a subcohort of 146 984 children (including 93 later registered with CP) born December 1998 through December 2001. Due to the small numbers, children with a gestational age of 37 and 38 weeks were grouped into one category as well as those with a gestational age of 42 through 44 weeks.