Risks Associated With Delivering Infants 2 to 6 Weeks Before Term—a Review of Recent Data

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SUMMARY

Background: There is an increasing trend towards delivery before 39 weeks of gestational age. The short- and long-term effects of early delivery on the infant have only recently received scientific attention.

Methods: Selective review of the literature

Results: Delivery at any time before 39 weeks is associated with significantly higher infant mortality and with an increase of the risk of impairments after birth from 8% to 11%. The increase in risks of various kinds is disproportionately more pronounced the earlier the child is delivered. For example, the risk of needing respiratory support or artificial ventilation after birth increases from 0.3% with delivery at 39–41 weeks of gestational age to 1.4% at 37 weeks and 10% at 35 weeks, while the risk of death or neurological complications increases from 0.15% at 39–41 weeks of gestation to 0.66% at 35 weeks. Delivery at 34.0 to 36.6 weeks of gestation also has long-term effects. Compared to delivery at term, the frequency of cerebral palsy rises threefold, from 0.14% to 0.43%; the risk of death in early adulthood rises by about half, from 0.046 to 0.065%; and the risk of dependence on government benefits in early adulthood also rises by about half, from 1.7% to 2.5%.

Conclusion: Studies from the USA have shown that the number of medically indicated deliveries before 39 weeks can be lowered by 70% to 80% through consistently applied measures for quality improvement. If similar results could be achieved in Germany, the iatrogenic complications of delivery would become less common in this country as well.

► Cite this as:

The number of infants born prematurely is increasing internationally (1). In Germany too, the percentage of infants discharged with the diagnosis “disorders connected with short duration of pregnancy and low birth weight” increased from 7.2% of all births in 2006 to 7.5% in 2010 (www.gbe-bund.de). Furthermore, between 2001 and 2007 the percentage of Cesarean sections rose from 21.6% to 29.3% of deliveries (2), which may also have contributed to an increase, not yet precisely quantified, in births occurring “only” 2 to 3 weeks before term. Overall, approximately 20% of all children born in Germany are 2 to 3 weeks pre-term, and 5% are 4 to 6 weeks pre-term (Figure 1).

Preterm infants are one of the largest patient groups in pediatrics. Whereas the treatment outcomes and long-term effects of very premature birth (less than 32 weeks’ gestation) have been fairly well researched (3), little is known about the short- or long-term developmental outcome of infants born 4 to 6 weeks before term. In Germany, the main reason for this is that perinatal and neonatal data are still not combined. It is also unclear whether births that occur 2 to 3 weeks before term can be taken to be as safe as full-term births.

As there are no controlled trials available on this subject, we aimed to compare data from epidemiological studies on the morbidity and mortality of infants born 2 to 6 weeks before term with those of full-term infants. To do this, we searched PubMed for articles from 2000 to May 2012 (search terms: “late preterm infant/birth,” “near-term infant/birth,” “outcome,” “mortality,” “morbidity,” “neurodevelopment”) and used only studies that were population-based or based on large networks and had been adjusted for confounding risk factors. Only statistically significant differences between groups (p <0.05) were subsequently included.

Morbidity and mortality in neonates born 2 to 3 weeks before term

For a long time it remained unclear whether any risk associated with birth occurring a few weeks before term should be attributed to an underlying disorder leading to preterm birth, to the mode of delivery (Cesarean section or spontaneous delivery) (4), or to premature birth.
Late preterm births: problems with neurological development

Turning to neurological development, the systematic review described above (7) showed that in the four studies it evaluated preterm infants born at 34\(^{0/7}\) to 36\(^{6/7}\) weeks’ gestation had three times the risk of developing cerebral palsy (0.43% versus 0.14%) and 1.5 times the risk of developmental delay at two years of age (0.81% versus 0.49%) (Table 3).

A further study showed that at two years of age children born at 34\(^{0/7}\) to 36\(^{6/7}\) weeks’ gestation had Bayley Test II mental or psychomotor development scores an average of between one and four points lower (9).

Late preterm births: development during school age and young adulthood

Mortality

Long-term studies often fail because many children are lost to follow-up. One exception is in Scandinavia, where every inhabitant can be tracked relatively easily using a single code number. For example, in Sweden a nationwide birth cohort consisting of singletons born at less than 37 weeks’ gestation between 1973 and 1979 was monitored up to the age of 29 to 36 years. This showed an increased risk of death for former preterm infants lasting into adulthood (Table 4) (10). This increased risk was independent of fetal growth delay or congenital malformations and mainly involved airway, endocrine, and cardiovascular disorders in those who died. This means that birth even a few weeks before term has a detectable negative effect on survival chances into adulthood. In order for such a conclusion to be valid, data must be painstakingly controlled for itself. This is a particularly important question when it comes to indicating elective Cesarean sections, when delivery date is usually determined jointly by the obstetrician and the mother. Evaluation of US data from 1999 to 2002 shed light on this subject (Table 1): singletons born by elective Cesarean section at 37 (i.e. 37\(^{0/7}\) to 37\(^{6/7}\)) weeks’ gestation showed twice the risk of dying or becoming acutely ill after birth compared to children born at 39\(^{0/7}\) to 39\(^{6/7}\) weeks’ gestation (Table 1). Even infants born at 38\(^{0/7}\) to 38\(^{6/7}\) weeks’ gestation had a 50% higher risk. 8% of infants born at 39\(^{0/7}\) to 39\(^{6/7}\) weeks’ gestation suffered at least one complication, compared to 15% of those born at 37\(^{0/7}\) to 37\(^{6/7}\) weeks’ gestation (5). These data were confirmed by a similar study in the Netherlands (6) (Table 1). Because such births are common, not normally performing scheduled Cesarean sections before 39 weeks’ gestation would have considerable consequences for medicine and health economics.

Late preterm births: mortality and neonatal morbidity

A systematic review evaluated studies from the years 2000 to 2010 on the health of infants born at 34 to 37 weeks’ gestation (Table 1). In nine papers on mortality, most of which were from the USA, 356 of 94 557 (0.38%) infants born at 34 to 37 weeks’ gestation died. In contrast, only 622 of 892 383 (0.07%) full-term infants died. Turning to morbidity, infants in the preterm group had higher incidences of airway disorders (respiratory distress syndrome, transient tachypnea, pulmonary hypertension, pneumothorax), infections (pneumonia, meningitis, sepsis, necrotizing enterocoli-
Mortality and serious adverse events in infants born at 37⁰⁷ to 40⁰⁷, ≥34⁰⁷, and 34⁰⁷ to 36⁰⁷ weeks’ gestation

<table>
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<th>Target parameter</th>
<th>Percentage</th>
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<td>2.4 (2.1 to 2.8)²⁷</td>
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<td>12.5</td>
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<td>33</td>
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¹ Inclusion criteria: elective, repeat Cesarean section between 1999 and 2002 in a hospital in the NICHD Neonatal Research Network; live singleton born at 37 to 40 weeks’ gestation.
² Data from Dutch birth statistics for 2000 to 2006 on live singletons born via elective Cesarean section after 37 to 40 weeks’ gestation in a hospital participating in the national follow-up program, excluding emergency Cesarean sections, births after complications of pregnancy potentially affecting the child, and congenital malformations.
³ Data from the birth statistics for the Burgundy region, on singleton births, with associated child and maternal data for 2000 to 2008.
⁴ Data from the birth statistics for the Hesse and Saarland region for 2001 to 2005 on singletons born via Cesarean section from a contraction-free uterus, excluding infant malformations of the heart or airways, chromosomal disorders, Apgar score <7/NaH <7.1, hydrops fetales, maternal alcohol/drug abuse; effect estimates given as nonadjusted relative risk.
⁵ SAE (serious adverse event) defined as birth and death or respiratory distress syndrome, transient tachypnea, hypoglycemia, neonatal sepsis, epileptic seizures, hypoxic-ischemic encephalopathy, CPR or ventilation in the first 24 hours after birth, umbilical artery pH <7.0, 5-minute Apgar score <5, admission to neonatal ICU, or hospital stay lasting 5 days or longer.
⁶ Relative risk adjusted for maternal age, race/ethnicity, no. of previous Cesarean sections, marital status, insurance status, smoking (yes/no), and diet-managed gestational diabetes.
⁷ SAE defined as need for reanimation, including intubation or NaHCO₃ administration, sepsis, respiratory distress syndrome, transient tachypnea, pneumothorax, need for oxygen or ventilation, hypoglycemia, seizure, brain hemorrhage, admission to ICU or hospitalization lasting more than 5 days, 5-minute Apgar score <5. Odds ratio adjusted for maternal age, ethnicity, no of previous births, socioeconomic status, sex of infant, and fetal position.
⁸ Disorder of the airways defined as respiratory distress requiring ventilation or CPAP. Neurological disorder defined as hypoxic-ischemic encephalopathy, intraventricular hemorrhage grade III/IV, cystic periventricular leukomalacia, or seizures. Effect estimates given as relative risk adjusted for all confounding factors that had a significant effect on the study variables in logistic regression.
⁹ Effect estimates stated as pooled relative risk using Review Manager 5.0.

GA: gestational age; SAE: serious adverse event
treatment for a psychiatric disorder (2.4% versus 2.6% versus 3.0% were affected) (13). Those born at 35.0/7 to 36.6/7 weeks’ gestation also had an increased risk of receiving inpatient treatment for epilepsy in early adulthood (0.7% versus 0.9%, adjusted odds ratio 1.76 [95% confidence interval, CI: 1.3 to 2.4]) (14). Finally, in a cohort of Swedish children born between 1987 and 2000, those born at 33.0/7 to 36.6/7 weeks’ gestation had a 30% higher risk (0.6% versus 0.8%) of pharmacologically treated attention deficit hyperactivity disorder (ADHD) than children born at 39.0/7 weeks’ gestation, and even those born at 37.0/7 to 38.6/7 weeks’ gestation had a risk approximately 10% higher (15).

Data on school performance and behavior
A Dutch group investigated 995 children born at 32.0/7 to 35.6/7 weeks’ gestation and a control group of 577 children born at term, using the Child Behavior Checklist. The former group had scores an average of four points lower for behavioral disorders and emotional problems (95% CI: 2.1 to 6.0), and twice the risk (7.9% versus 4.6%) of abnormal findings in these areas, when compared to controls (16). Another Dutch group investigated 377 children born at 32.0/7 to 36.6/7 weeks’ gestation in terms of their success at school at an average age of 8.9 years. 9.7% of children born at 32 to 33 weeks’ gestation, 7.3% of those born at 34 to 35 weeks’ gestation, and 2.8% of control group children attended special schools; of those who attended regular schools, those who had been born before term were twice as likely to have already had to repeat a grade (19% versus 8%) (17).

Three recent studies in the UK confirm the Dutch data. In one of these, teachers of 7650 children who were representative of children of their age in Great Britain as a whole rated the extent to which their pupils had attained the targets set for them at the end of their first year of school. Children born at 34.0/7 to 36.6/7 weeks’ gestation had a 12% higher risk of not having performed successfully at the end of their first year of school; even children born at 37.0/7 to 38.6/7 weeks’ gestation had a higher risk of this than those born at 39.0/7 to 40.6/7 weeks’ gestation (18). The second study investigated 12,089 children born at term and 734 children born at 32.0/7 to 36.6/7 weeks’ gestation. Those born before term had 1.4 times the risk (21% versus 29%) of poor school performance at the end of their second year of school; analyzing only children born at 34.0/7 to 36.6/7 weeks’ gestation did not substantially change this result (19). Finally, evaluation of the school performance of 407,503 Scottish schoolchildren showed that those born at 33.0/7 to 36.6/7 weeks’ gestation had 1.5 times the risk (4.3% versus 6.5%) of requiring special educational support (20). In this study too, the risk was higher even for children born at 37.0/7 to 38.6/7 weeks’ gestation than for those born at term.

Only one study on long-term cognitive performance did not confirm the above results. This study involved nearly 1300 children born at 34.0/7 to 36.6/7 weeks’ gestation and excluded a priori children with neonatal health problems (defined as a hospital stay lasting longer than seven days or a congenital disorder) and those living in severely socially disadvantaged environments. Evaluation of the questionnaire used to investigate the children found no “consistently significant” differences between this selected group and a control group of children born at 37.0/7 to 41.5/7 weeks’ gestation (21).

To summarize, these data allow us to conclude that birth even a few weeks before term is associated with increased mortality or morbidity as follows:

- Neonatally
- In early adulthood
- With an increased risk of requiring admission to a neonatal ICU
- With an increased risk of entitlement to welfare benefits in early adulthood
- Or poor performance or need for special educational support at elementary school.

However, observational studies cannot prove a causal relationship, and almost none of the studies described here was conducted in Germany. Nevertheless,

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<td>RDS</td>
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<td>10.2 (9.44 to 10.9)</td>
</tr>
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<td>RDS</td>
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<td>6.49 (6.08 to 6.93)</td>
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<tr>
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<td>106 833</td>
<td>RDS</td>
<td>1.17</td>
<td>3.61 (3.41 to 3.82)</td>
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<td>RDS</td>
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</table>

1 Data source: Centers for Disease Control, n = 175 112 datasets after 34 to 36 WG versus 2 992 503 datasets after 37 to 40 WG. Inclusion criteria: singleton, pregnancy free from complications caused by maternal cardiac, pulmonary, or renal disease, no gestational hypertonus/pre-eclampsia, (gestational) diabetes, premature rupture of membranes, placental abruption, or placenta previa.

2 Adjusted for maternal age, no. of previous births, race/ethnicity, maternal level of education, weight increase during pregnancy, no. of antenatal checkups, and no. of cigarettes/day.

GA: gestational age; WG: weeks’ gestation; RDS: respiratory distress syndrome; NN: neonatal infection
elective deliveries before 390/7 weeks’ gestation, stillbirths remained unchanged during the study period.

The total number of deliveries and the percentage of full-term neonates born decreased. For elective deliveries, a US hospital operator implemented a quality improvement initiative to address this issue and in 27 hospitals compared the rate of elective deliveries (induced labor or Cesarean section) before and after introduction of three different procedures to reduce the percentage of such deliveries: 

- Group 1: a clear prohibition on setting dates of delivery before 390/7 weeks’ gestation
- Group 2: advising against delivery before 390/7 weeks’ gestation, but leaving the decision on date of delivery to individual doctors
- Group 3: an information campaign on the risks of preterm delivery.

Within two years, the percentage of elective deliveries fell from 9.6% to 4.3% (p<0.001). The decrease was greatest in group 1: In this group only 1.7% of all elective deliveries still occurred after 390/7 weeks’ gestation, whereas in groups 2 and 3 this figure was 3.3% and 6.0%, respectively. The percentage of full-term neonates requiring intensive care fell from 8.9% to 7.5%. The total number of deliveries and the percentage of stillbirths remained unchanged during the study period (22). An even more marked drop in the percentage of elective deliveries before 390/7 weeks’ gestation, specifically from 28% to 3% or less, was described in a hospital association in Utah. This was also brought about by a combination of explanation and prohibition; again, no disadvantages for mother or child were recorded (23). These examples clearly show that the number of preterm elective deliveries can be reduced comparatively easily and with no disadvantages for patients; this is likely to be true for Germany, too.

The data summarized here show clearly that there remains an urgent need to test ideas to reduce elective preterm deliveries in order to determine whether they are also suitable for Germany, and at the same time to develop methods to prevent preterm births. In doing so, a distinction must be made between fetomaternal and nonmedical reasons for setting a date of delivery: Only the latter should change. In addition, the current definition of preterm birth must be questioned: It implies that a distinction must be made between fetomaternal and nonmedical reasons for setting a date of delivery: Only the latter should change. In addition, the current definition of preterm birth must be questioned: It implies that an infant born at 370/7 to 386/7 weeks’ gestation is full-term and therefore has no greater risk of peripartum complications than an infant born at 390/7 weeks or more, and according to the data summarized here this is clearly untrue.

The data presented here raise the question of whether the percentage of preterm deliveries can be reduced. For elective deliveries, a US hospital operator implemented a quality improvement initiative to address this issue and in 27 hospitals compared the rate of elective deliveries (induced labor or Cesarean section) before 390/7 weeks’ gestation before and after introduction of three different procedures to reduce the percentage of such deliveries:

- Group 1: a clear prohibition on setting dates of delivery before 390/7 weeks’ gestation
- Group 2: advising against delivery before 390/7 weeks’ gestation, but leaving the decision on date of delivery to individual doctors
- Group 3: an information campaign on the risks of preterm delivery only.

The data summarized here show clearly that there remains an urgent need to test ideas to reduce elective preterm deliveries in order to determine whether they are also suitable for Germany, and at the same time to develop methods to prevent preterm births. In doing so, a distinction must be made between fetomaternal and nonmedical reasons for setting a date of delivery: Only the latter should change. In addition, the current definition of preterm birth must be questioned: It implies that an infant born at 370/7 to 386/7 weeks’ gestation is full-term and therefore has no greater risk of peripartum complications than an infant born at 390/7 weeks or more, and according to the data summarized here this is clearly untrue.

Conflicts of interest statement

Prof. Wallwiener and Prof. Vetter declare that no conflict of interest exists.
Prof. Poets declares that he has received fees for arranging scientific continuing education events from Milupa. He has also received reimbursement of expenses for data collection and payment for a research project he himself initiated from Chiesi.

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References

KEY MESSAGES

- Approximately 20% of all births in Germany occur at 37 to 38 weeks’ gestation. Approximately 5% occur at 34 to 36 weeks’ gestation.
- The risk of death or neurological complications rises from 0.15% for births at 36 weeks’ gestation to 0.86% for births at 35 weeks’ gestation.
- Long-term effects of preterm birth include an association with a 50% rise, from 1.7%, to 2.5%, in the risk of entitlement to welfare benefits in early adulthood.
- This may be connected with the higher percentage of children requiring special educational support in elementary school: 4.3% of children born at full term versus 6.5% of children born before term at 33 to 36 weeks.
- US studies show that the percentage of deliveries occurring before 39 weeks can be reduced from over 20% to ≤3% using administrative measures. On the basis of the data stated above, this should also be encouraged in Germany.


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