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Infant mortality at term in Canada: Impact of week of gestation

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ABSTRACT

Objectives: Infants born at term have low mortality, but risk may vary from week to week. We determined the risk of infant mortality at term by gestational week and cause.
Methods: We analyzed 4.1 million infants born at ≥37 weeks of gestation in Canada from 1991 to 2010, followed for mortality the first year of life. We estimated hazard ratios (HR) and 95% CIs for early, late and post neonatal mortality from 37 through 41 weeks of gestation, adjusting for individual characteristics. The main outcomes were mortality due to congenital anomaly, asphyxia, immaturity, infection, sudden infant death, and injury.
Results: Infant mortality decreased progressively from 4.55 per 1000 at 37 weeks to 1.62 per 1000 at 41 weeks. Early neonatal mortality varied little between 39 and 41 weeks, but post neonatal mortality was lowest at 40–41 weeks. Relative to 41 weeks of gestation, mortality at 39 weeks was higher for congenital anomaly (HR 1.30, 95% CI 1.05–1.60) and sudden infant death (HR 1.58, 95% CI 1.18–2.11).
Conclusion: In Canada, mortality at term is lowest for infants born at 40 or 41 weeks of gestation, especially at late and post neonatal ages, and for congenital anomaly and sudden infant death.

1. Introduction

Infant mortality receives attention worldwide. In wealthy countries, up to 7 infants per 1000 do not make it past the first year of life [1]. In Canada, about 5 infants per 1000 do not survive to 1 year [2]. Mortality during infancy is higher than at any other point during childhood [3]. The burden of infant death has spurred a search for factors associated with mortality, including length of gestation [4]. Much attention has been paid to the gestational age at which infants are born, especially the preterm period. Infants born preterm have very high rates of mortality, and moderate preterm births account for a large fraction of these deaths [5].

However, preterm infants account for no more than a tenth of births [2,6], whereas infants born at term are more numerous and account a third of infant deaths [7,8], despite their gestational age advantage. Studies increasingly report that the period spanning term is not homogeneous [9], and that morbidity and mortality are higher for infants born early (37 and 38 weeks) rather than full term (39 to 41 weeks) [10–14]. A recent report suggested that risks may even vary during full term, with mortality of infants born at 39 weeks potentially higher than at 40 weeks [15], though this finding was not corroborated in other studies [16,17]. This research is only beginning, however, and little is known on whether gestational age at term is associated with the age of infants at time of death (i.e., early, late, or post neonatal), or the cause of mortality. To help bridge this knowledge gap, we sought to determine how infant mortality in Canada varied with each week at term, defined as 37 weeks of gestation or more. We investigated infant mortality by age and cause of death.

2. Material and methods

2.1. Population and study design

We extracted data on the cohort of 4.1 million singleton neonates born at 37 weeks of gestation or more from Statistics Canada's Infant Birth-Death Linked File, created through linkage of death records of infants younger than one year of age with birth records. This file was validated by the Canadian Perinatal Surveillance System [18], and recently updated to cover all births from 1991 through 2010, including 8700 infant deaths at term. Neonates in the cohort were followed for mortality during the first year of life, with cause of death documented using the 10th revision of the International Classification of Diseases (ICD) from death registration certificates. We did not include the province of Ontario in our analysis, due to incomplete registration of births at potentially higher risk of mortality [2]. Preterm births were not considered because

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risks of infant mortality before 37 weeks of gestation are well documented elsewhere [19,20].

We used the completed number of weeks of gestation as the main exposure, such that 38 weeks, for example, included all neonates born between 38^{+0} and 38^{+6} days of gestation. In Canada, gestational age is typically based on clinical estimates, using ultrasound examinations in the first or second trimester of pregnancy [21]. Menstrual dating is less commonly used, minimizing misestimates of gestational age [22].

The main outcome measure was infant mortality in the early, late, or post neonatal periods. The early neonatal period was defined as the first 0 to 6 days of life, late neonatal as 7 to 27 days, and post neonatal as 28 through 364 days of life. Cause of infant death was classified using the method proposed by Cole et al. to facilitate international comparisons [23]. There were seven groups of causes, including death from 1) congenital anomaly, 2) asphyxia, 3) conditions related to immaturity, 4) infection, 5) sudden infant death syndrome, 6) external injury, and 7) other causes. ICD codes for these causes were taken from national sources [2]. Cause of death was only available for infants born during the latter half of the study, from 2000 onward.

Covariates available in the data, selected for their potential to influence the relation between gestational age at time of birth and risk of mortality at term, included maternal age (<20, 20–29, 30–34, ≥35 years), marital status (married, single, divorced/separated/widowed), parity (0, 1, ≥2 previous deliveries), birth region (British Columbia, Prairies, Quebec, Atlantic, Territories), and period (1991–1995, 1996–2000, 2001–2005, 2006–2010).

2.2. Data analysis

We computed mortality rates per 1000 births during each week at term. In addition, we calculated the cumulative mortality rate at each week per 1000 total births. We examined the distribution of infant deaths by week of gestation for all causes, and by specific cause of death since 2000.

We analyzed the data prospectively, using a time-to-event design. In Cox regression models, we estimated hazard ratios (HR) and 95% confidence intervals (CI) for infant mortality at each week of gestation using 41 weeks as the reference, as risks were lowest at this time. Models were adjusted for maternal age, marital status, parity, region, and period. The time scale was defined as number of days of life since birth. For early neonatal mortality, follow-up began at birth, or 0 days, and ended at 6 days of life. For late neonatal mortality, follow-up began at 7 and ended at 27 days. For late neonatal mortality, follow-up began at 28 and ended at 364 days of life. Finally, we modelled infant mortality overall, with follow-up beginning at birth and ending at 364 days. The proportional hazards assumption was verified visually using plots of log (− log survival) curves.

To determine cause-specific risks of mortality, we computed HRs separately for congenital anomaly, asphyxia, conditions related to immaturity, infection, sudden infant death, injury, and other causes. These analyses were restricted to infants born after 2000 when data on cause of death were available. In each model, we censored deaths from all other causes [24].

In sensitivity analyses, we verified that associations were similar in both adjusted and unadjusted models, and when data included multiple births. We examined associations for early, late and post neonatal mortality for each calendar period, to ensure that the findings were stable over time.

Data analyses were carried out in SAS 9.3 (SAS Institute Inc., Cary, NC). The linked live births and deaths file was created with approval of provincial and territorial vital statistics registrars in Canada. The institutional review board of the University of Montreal Hospital Centre waived the requirement for ethical review of the current study, as the data were anonymous and analysis conformed to rules for ethical conduct of research involving humans in Canada.

3. Results

There were 2450 early neonatal, 1270 late neonatal, and 4990 post neonatal deaths during study follow-up. Infant mortality for singletons at term was 2.15 per 1000 births overall (95% CI 2.10–2.20) (Table 1). Rates tended to decrease over time, varied across regions, and were higher for infants born to young, single, and multiparous women. Rates of early, late, and post neonatal mortality were 0.60, 0.31, and 1.23 per 1000, respectively.

Mortality was highest for infants born at 37 weeks of gestation (4.55 per 1000; 95% CI 4.29–4.81), with rates declining progressively to 1.62 per 1000 at 41 weeks (95% CI 1.52–1.72) before rising thereafter (Table 2). The same was found for post neonatal mortality, which was highest at 37 weeks and decreased steadily to 41 weeks before peaking again. For late neonatal mortality, the decrease reached a nadir earlier, with 0.23 deaths per 1000 at 40 weeks (95% CI 0.20–0.26) compared with 0.30 at 39 weeks (95% CI 0.27–0.33). Early neonatal mortality reached a low even earlier, with 0.49 deaths per 1000 at 39 weeks (95% CI 0.45–0.53) compared with 0.72 at 38 weeks (95% CI 0.66–0.78).

However, the cumulative rate of infant mortality increased throughout term, though most deaths occurred between 38 and 40 weeks of gestation (Table 2). The fraction of deaths was largest at 40 weeks for early and post neonatal mortality, and between 38 and 40 weeks for late neonatal mortality.

The adjusted risk of infant mortality was nearly 3 times higher at 37 weeks (HR 2.79, 95% CI 2.56–3.03), and 2 times higher at 38 weeks (HR 1.74, 95% CI 1.61–1.88), relative to 41 weeks of gestation (Table 3). In addition, the risk at 39 weeks was 22% greater (HR 1.22, 95% CI 1.13–1.32). The risk at 40 weeks was not statistically distinguishable from 41 weeks, but did tend to be elevated slightly. The progressive trend over gestational age was most apparent at late neonatal ages, but also present at post neonatal ages. For early neonatal mortality, risks were more pronounced at 37 and 38 weeks.

At term, the leading causes associated with highest infant mortality rates were congenital anomalies at 0.56 deaths per 1000 and sudden infant death syndrome at 0.29 per 1000 (Table 4). Asphyxia and infection were each responsible for additional 0.15 deaths per 1000. Not surprisingly, conditions linked with immaturity were rare (0.05 per 1000), as were injuries (0.06 per 1000). For each of these causes, the mortality rate was higher at 37 weeks than at 41 weeks.

For congenital anomaly, rates cumulated steadily up to 41 weeks, suggesting that anomalies were an important cause of death throughout term (Table 4). The majority of deaths due to anomalies were distributed evenly between 38 and 40 weeks. For the remaining causes, rates cumulated disproportionately earlier during term. However, deaths due to birth asphyxia and injury tended to be shifted later in term, with a lower proportion occurring at 37 or 38 weeks.

At 37 weeks of gestation, the risk of mortality was higher for all seven causes of death, and tended to decrease progressively to 41 weeks thereafter (Table 5). At 39 weeks, the two causes associated with the highest risk of death relative to 41 weeks were congenital anomaly (HR 1.30, 95% CI 1.05–1.60) and sudden infant death (HR 1.58, 95% CI 1.18–2.11). At 40 weeks, risk of mortality was not statistically distinguishable from 41 weeks for any cause, except death from other causes (HR 1.52, 95% CI 1.02–2.26).

In sensitivity analyses, models not adjusted for maternal age, marital status, parity, region, and period yielded similar associations (data not in tables). In unadjusted models, the risk of infant mortality at 40 weeks was 8% higher relative to 41 weeks (unadjusted HR 1.08, 95% CI 1.00–1.16). Splitting by neonatal age indicated that much of the elevated risk was attributable to the late neonatal period (unadjusted HR 1.11, 95% CI 1.01–1.23). Inclusion of multiple births had little impact on associations. The risk of early neonatal death during term decreased over time whereas risk of late neonatal death increased. The risk of early neonatal mortality in infants born at 38 weeks, for example, decreased from a HR of 1.86 (95% CI 1.48–2.34) in 1991–1996 to