Relationship of Prenatal Diagnosis and Pregnancy Termination to Overall Infant Mortality in Canada

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INFANT MORTALITY RATES HAVE DECLINED dramatically during the last few decades in most industrialized countries.\(^\text{1-6}\) Between 1991 and 1995, however, Canadian infant mortality rates stagnated between 6.1 and 6.4 per 1000 live births.\(^\text{7}\) In fact, the infant mortality rate in 1993 (6.3 per 1000 live births) was higher than the infant mortality rate in 1992 (6.1 per 1000 live births), a phenomenon that had not occurred for 3 decades. The trends in Canadian infant mortality rates in the early 1990s, especially the increase in 1993, have been attributed to the increasing registration of live births at the borderline of viability (eg, birth weight <500 g).\(^\text{8}\)

The infant mortality rate dropped substantially to 5.6 per 1000 live births in 1996 and to 5.5 per 1000 live births in 1997 in Canada.\(^\text{9,10}\) The reason for this marked decline is unclear. We carried out a study to examine 3 potential explanations: (1) a reversal of birth registration patterns pertaining to live births with birth weights less than 500 g; (2) a global (ie, all-cause) decrease in infant deaths; and (3) a decline in specific causes of infant death.

We were particularly interested in examining the impact of declines in infant deaths due to congenital anomalies. Recent advances in prenatal diagnosis and selective termination of affected pregnancies have led to declines in the birth prevalence of congenital anomalies and to decreases in infant deaths due to congenital anomalies. A large decrease in infant deaths due to congenital anomalies was associated with the most recent decline in infant mortality in Canada, suggesting that increases in prenatal diagnosis and pregnancy termination for congenital anomalies are related to decreases in overall infant mortality at the population level.

Context Prenatal diagnosis and termination of affected pregnancies can prevent infant deaths due to congenital anomalies, but an effect at the population level has not been shown.

Objective To examine the impact of recent changes in congenital anomaly–related fetal and infant deaths on overall population-based infant mortality.


Main Outcome Measures Cause-specific infant mortality rates and gestational age–specific fetal death rates.

Results The birth cohort–based infant mortality rate fluctuated between 6.4 and 6.1 per 1000 live births between 1991 and 1995, then dropped to 5.4 per 1000 in 1996 and 5.5 per 1000 in 1997. The rate of infant death from congenital anomalies was stable between 1991 and 1995 but declined by 21% (95% confidence interval, 19%-32%) from 1.86 per 1000 in 1995 to 1.47 per 1000 in 1996 and 1997. Fetal deaths due to pregnancy termination at 20 to 23 weeks’ gestation increased dramatically in 1994, while fetal deaths due to congenital anomalies at 20 to 21 weeks increased in 1995 and subsequently. Provinces/territories with high rates of fetal death due to pregnancy termination/congenital anomalies at 20 to 23 weeks had fewer infant deaths due to congenital anomalies.

Conclusion A large decrease in infant deaths due to congenital anomalies was associated with the most recent decline in infant mortality in Canada, suggesting that increases in prenatal diagnosis and pregnancy termination for congenital anomalies are related to decreases in overall infant mortality at the population level.

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for the underlying cause of death.\textsuperscript{22} The ICE on Perinatal and Infant Mortality cause-of-death categories include congenital conditions, immaturity-related conditions, asphyxia-related conditions, infections, other specific conditions, sudden infant death syndrome (SIDS), external causes, and remaining causes.\textsuperscript{22,23} Although this classification is helpful as a broad classification scheme for causes of infant death, the ICE category of congenital conditions is not widely used for identifying congenital anomalies. Because the focus of our study was related to congenital anomalies (and pregnancies that could be terminated following prenatal diagnosis), we also calculated rates of infant deaths due to congenital anomalies (ICD-9 codes 740-759). For causes of fetal death, we specifically focused on congenital anomalies as well as termination of pregnancy (ICD-9 code 779.6).

Traditionally, infant mortality rates are calculated as ratios by dividing the number of infant deaths in a calendar year by the number of live births in the same (index) year. The overall or cause of death–specific infant mortality rates described in this study were based on birth cohorts and represent the proportion of infants who died before age 1 year among live births in the year of interest. This change in the method of computing infant mortality means that the temporal patterns of infant mortality presented in this study differ slightly from those reported by Statistics Canada and presented in the introduction of this article. Thus, we first calculated crude infant mortality rates (ie, including all live births and infant deaths) to present an overall infant death profile. We then examined changes in the registration of live births with weight of less than 500 g and the effect of such changes on infant mortality. Subsequent analyses of cause of death–specific infant mortality rates were restricted to live births with weights of 500 g or more.

We also examined stillbirth rates by gestational age to assess whether any potential decline in infant mortality due to congenital anomalies was temporally preceded by increases in pregnancy terminations or early-gestation (20-21 weeks) stillbirths due to congenital anomalies. We assumed that recent temporal increases in fetal deaths due to congenital anomalies at 20 to 21 weeks’ gestation would be due to prenatal diagnosis and termination. In Canada, between 1991 and 1998, the distinction between an abortion and a fetal death was made using a gestational age cutoff of 20 weeks or more, a birth weight cutoff of 500 g or more, or both. Most Canadian provinces and territories (Nova Scotia, Manitoba, Alberta, British Columbia, Yukon, and the Northwest Territories; Saskatchewan prior to 1994) defined a stillbirth as a fetal death at a gestational age of 20 weeks or more or a birth weight of 500 g or more. A few provinces (Newfoundland, New Brunswick, and Quebec; Saskatchewan since 1994) relied exclusively on the birth weight criterion, while Prince Edward Island used the gestational age criterion exclusively.\textsuperscript{24} All fetal deaths satisfying the stillbirth definition were required by law to be registered. Pregnancies affected by major congenital anomalies and terminated following prenatal diagnosis were registered as stillbirths unless the procedure was carried out prior to 20 weeks or at least 500 g (or if the fetus was live born). Gestational age–specific fetal death rates were estimated per 100 000 fetuses at risk (ie, all fetuses stillborn or live born at that or a later gestational age).

Supplementary analyses were also carried out on live births and infant deaths that occurred in 1998 to ascertain whether the patterns observed in the birth cohorts of previous years were also manifested among births and deaths in this calendar year (the 1998 birth cohort could not be created because information on infant deaths in 1999 was not available). Specifically, we calculated fetal death rates (by cause) as well as the proportion of live births with weights of less than 500 g in 1998. Finally, we carried out an analysis by province/territory to determine whether rates of fetal death due to congenital
anomalies/pregnancy termination were associated with infant mortality rates. All provincial registries follow common federal standards, and provincial data are generally comparable. We restricted this analysis to 1994-1997 because the effects first became apparent in 1994.

The significance of temporal changes was estimated using relative risks, risk reductions, and 95% confidence intervals (CIs). The \( \chi^2 \) test for linear trend in proportions was used to guide the assessment of temporal trends. Two-sided \( P \) values were calculated and exact binomial 95% CIs were estimated for relevant rates. All analyses were carried out using SAS, version 8 (SAS Inc, Cary, NC).

**RESULTS**

The birth cohort–based infant mortality rate (including births <500 g) fluctuated between 6.4 and 6.1 per 1000 between 1991 and 1995, then declined to 5.4 per 1000 in 1996 and 5.5 per 1000 in 1997 (Table 1). The rate of live births of less than 500 g increased from 6.0 per 10000 live births in 1991 to 9.0 per 10000 in 1997, then declined to 7.7 per 10000 in 1998 (.001 for trend). Among live births of 500 g or more, infant mortality rates ranged between 5.3 and 5.7 per 1000 live births for 1991-1993, then declined dramatically and remained at 4.5 per 1000 live births for 1996 and 1997 (Table 1).

Examination of infant mortality rates within cause-of-death categories (live births ≥500 g) showed that congenital anomalies were the major cause of infant mortality between 1991 and 1997. Most causes of death, particularly SIDS and immaturity, showed a decreasing trend between 1991 and 1997 (Table 2). Infant mortality due to SIDS declined steadily from 1.07 per 1000 live births in 1991 to 0.85 per 1000 live births in 1995. The rate of infant death from congenital anomalies did not change between 1991 and 1995, then declined by 21% (95% CI, 19%-32%) from 1.86 per 1000 live births in 1995 to 1.47 per 1000 live births in both 1996 and 1997.

Examination of gestational age–specific fetal death rates showed that fetal deaths at 20 to 21 weeks’ gestation increased from 51.1 per 100000 fetuses at risk in 1991 to 86.0 per 100000 fetuses at risk in 1998 (.001 for trend). This increase was due to increases in fetal deaths due to congenital anomalies at 20 to 21 weeks gestation, which increased by 94% (95% CI, 14%-229%) from 8.8 per 100000 fetuses at risk in 1991 to 17.1 per 100000 fetuses at risk in 1998 (.001 for trend). Fetal deaths due to pregnancy termination at 20 to 21 weeks increased by 578% (95% CI, 220%-1335%) from 3.2 per 100000 in 1991 to 20.9 per 100000 fetuses at risk in 1997.

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1998 (P<.001 for trend for 1991-1998). The increase in fetal deaths due to congenital anomalies at 20 to 21 weeks began in 1994, while the increase in fetal deaths due to pregnancy termination began in 1995 (Table 3). The fetal death rate due to pregnancy termination at 22 to 23 and 24 to 27 weeks' gestation also showed an increasing trend from 1991 to 1998, especially after 1995 (P<.001 for trend for 1991-1998). However, the fetal death rate due to congenital anomalies remained unchanged at 22 to 23 and 24 to 27 weeks' gestation (P=.22 and .39 for trend, respectively). Fetal deaths due to other causes at 24 to 27 weeks' gestation decreased significantly (P<.001 for trend; Table 3).

The increases in fetal deaths due to congenital anomalies at early gestational age were accompanied by decreases in fetal deaths due to congenital anomalies at later gestational ages (Table 3). Fetal deaths due to congenital anomalies at 28 to 36 weeks decreased significantly from 23.9 per 100000 in 1991 to 15.3 per 100000 fetuses at risk in 1998 (P=.02 for trend), while fetal deaths due to congenital anomalies at 37 weeks or more declined nonsignificantly (P=.13 for trend). The decline in the overall rate of fetal death during the 8-year study period was nominally significant (P=.05 for trend).

Regional (ecological) comparisons showed that provinces/territories with high rates of fetal death due to pregnancy termination/congenital anomalies at 20 to 23 weeks' gestation had fewer infant deaths due to congenital anomalies (Figure). For example, in Saskatchewan, the rate of fetal death due to pregnancy termination/congenital anomalies at 20 to 23 weeks was 16.7 per 100000 fetuses at risk, while the rate of infant mortality due to congenital anomalies was 2.57 per 100000 live births.

Table 3. Fetal Death Rates per 100,000 Fetuses at Risk According to Gestational Age Due to Congenital Anomalies, Pregnancy Termination, and Other Causes, Canada Excluding Ontario, 1991-1998*

<table>
<thead>
<tr>
<th>Birth Cohort</th>
<th>Gestational Age 20-21 wk</th>
<th>Gestational Age 22-23 wk</th>
<th>Gestational Age 24-27 wk</th>
<th>Gestational Age 28-36 wk</th>
<th>Gestational Age ≥37 wk</th>
<th>All Gestational Ages*</th>
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<tr>
<td>Congenital anomalies</td>
<td>22</td>
<td>8.8</td>
<td>26</td>
<td>10.6</td>
<td>26</td>
<td>10.9</td>
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<tr>
<td>Pregnancy termination</td>
<td>8</td>
<td>3.2</td>
<td>2</td>
<td>0.8</td>
<td>1</td>
<td>0.4</td>
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<tr>
<td>Other</td>
<td>97</td>
<td>39.0</td>
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<tr>
<td>Total</td>
<td>127</td>
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<td>54.0</td>
<td>126</td>
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<tr>
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<td>32</td>
<td>13.0</td>
<td>20</td>
<td>8.4</td>
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<tr>
<td>Pregnancy termination</td>
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<td>1.2</td>
<td>5</td>
<td>2.0</td>
<td>2</td>
<td>0.8</td>
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<td>Other</td>
<td>165</td>
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<td>55.3</td>
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<td>50.1</td>
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<td>Total</td>
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<td>70.3</td>
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<tr>
<td>Pregnancy termination</td>
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<td>0.8</td>
<td>3</td>
<td>1.2</td>
<td>1</td>
<td>0.4</td>
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<td>75.3</td>
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<td>23.9</td>
<td>60</td>
<td>24.5</td>
<td>53</td>
<td>22.2</td>
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<tr>
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<td>179.1</td>
<td>416</td>
<td>169.9</td>
<td>378</td>
<td>158.6</td>
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<tr>
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<td>476</td>
<td>194.4</td>
<td>431</td>
<td>149.4</td>
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<tr>
<td>Congenital anomalies</td>
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<td>30</td>
<td>11.3</td>
<td>26</td>
<td>11.7</td>
</tr>
<tr>
<td>Other</td>
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<td>168.1</td>
<td>380</td>
<td>166.0</td>
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<td>170.8</td>
</tr>
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<td>410</td>
<td>179.1</td>
<td>407</td>
<td>182.5</td>
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</tbody>
</table>

*Fetal deaths and live births of less than 500 g included in the calculation of fetal death rates.
†Live births and fetal deaths with unknown gestational age were included. There were 29, 1, and 206 fetal deaths with unknown gestational age due to congenital anomalies, pregnancy termination, and other causes, respectively, between 1991 and 1998. The numbers of fetal deaths due to congenital anomalies with unknown gestational age from 1991 through 1998 were 2, 3, 7, 6, 6, 1, 3, and 1, respectively.

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1000 live births. In contrast, in Nova Scotia, where the rate of fetal death due to pregnancy termination/congenital anomalies at 20 to 23 weeks was 131.4 per 100000 fetuses at risk, the rate of infant mortality due to congenital anomalies was 1.35 per 1000 live births.

COMMENT

Our study shows that infant mortality rates among Canadian birth cohorts stagnated between 1991 and 1995, declined dramatically in 1996, and remained low in 1997. These declines in infant mortality are particularly impressive because they occurred against a background of steady increases in the registration of live births with weights of less than 500 g (from 6.0 per 10000 live births in 1991 to 9.0 per 10000 in 1997). Between 1991 and 1995, infant mortality declined among live births of 500 g or more occurred in several cause-of-death categories, including SIDS and immaturity, but not in deaths due to congenital anomalies. The patterns changed abruptly in 1996 and 1997, however. A reduction in infant deaths due to congenital anomalies was associated with the sharp decline in overall infant mortality in the 1996 and 1997 birth cohorts.

The decrease in infant deaths due to congenital anomalies in 1996 was temporally preceded by an increase in fetal deaths due to congenital anomalies at 20 to 21 weeks’ gestation. Fetal deaths due to congenital anomalies at 20 to 21 weeks’ gestation increased dramatically in 1994, while fetal deaths due to pregnancy termination at 20 to 21 weeks increased dramatically in 1995. Although information on the exact reasons for termination of pregnancy is not available, the data suggest that increasing use of prenatal diagnosis for major congenital anomalies and selective termination of affected pregnancies has led to perceptible declines in infant mortality in Canada. The observed 4-fold increase in fetal deaths due to both congenital anomalies and pregnancy termination at 20 to 21 weeks’ gestation almost certainly underestimates the total contribution of prenatal diagnosis and termination. Since termination of affected fetuses is usually carried out prior to 20 weeks’ gestation, many such terminations would not be classified as stillbirths. In fact, the increase in fetal deaths due to congenital anomalies at early gestational ages (20–21 weeks) is only an approximate indicator of the magnitude of the increase in prenatal diagnosis and selective pregnancy termination. It is likely that even between 1994 and 1998, there was an increasing trend toward earlier prenatal diagnosis/pregnancy termination, coupled with a substantial increase in the frequency of prenatal diagnosis/pregnancy termination. This probably explains the lag period between the increase in fetal deaths due to congenital anomalies (first observed in 1994) and pregnancy termination at early gestational ages (first observed in 1995) and the decline in infant mortality (first observed in 1996). Our findings are further supported by the regional patterns of the relationship between fetal deaths due to congenital anomalies/pregnancy termination at 20 to 23 weeks and infant deaths due to congenital anomalies. Although prenatal diagnosis and pregnancy termination are insured services under Canada’s universal health care insurance program, the availability and uptake of such services are variable and depend on local factors. Provinces/territories such as Saskatchewan, which did not have a widespread prenatal screening program, had higher rates of infant death due to congenital anomalies. In this context, it is noteworthy that temporal changes in rates of infant mortality due to congenital anomalies among whites and nonwhites in the United States have been attributed in part to differences in access to prenatal diagnosis. Rates of infant death due to congenital malformations were higher among whites than nonwhites in 1970-1971 (3.1 vs 2.6 per 1000 live births), but the differential has reversed in recent years (1.6 and 1.7 per 1000 live births among whites vs nonwhites in 1996-1997).
During the last few decades, medical advances and improved perinatal care have led to a substantial decrease in infant deaths due to respiratory distress syndrome, sepsis, and asphyxia.26-28 Public health campaigns (eg, public education) regarding sleeping position have also contributed to reducing the risk of SIDS considerably.29,30 As a consequence, the relative proportion of infant deaths due to congenital anomalies has risen considerably, and congenital anomalies have emerged as a leading cause of death in both the neonatal and the postneonatal periods in Canada and other industrialized countries.28,31-34 In Canada, infant deaths due to congenital anomalies constitute approximately 30% of all infant deaths.28 Prenatal diagnosis and pregnancy termination for congenital anomalies have increased in recent years1,3,16,12,15 and have led to marked reductions in the birth prevalence of congenital anomalies.2,19,36 The widespread availability of prenatal diagnosis for severe congenital anomalies and subsequent early termination of affected pregnancies have led to sharp declines in late fetal and infant deaths due to congenital anomalies. As this technology improves, with second-trimester screening giving way to first-trimester screening,37,38 and as prenatal diagnosis of congenital anomalies gains wider access in rural areas,28 the rate of infant mortality due to congenital anomalies can be expected to decline further.

Other potential factors that could be responsible for the decrease in infant deaths from congenital anomalies include improvements in surgical and other interventions aimed at correcting congenital abnormalities40 and an increase in periconceptional folic acid supplementation. However, folic acid supplementation is an unlikely explanation for the observed decrease. First, observed patterns of gestational age-dependent and congenital anomaly-specific change in fetal and infant death (eg, reductions in congenital anomalies of the central nervous system, cardiovascular system, urinary system) are more consistent with increases in prenatal diagnosis and termination than with primary preventive effects.11 Second, studies have suggested limited knowledge regarding the protective effects of folic acid among Canadian women during the study period.41 This was a major factor leading to food fortification with folic acid since 1998.42

During the last 2 decades, the ability to diagnose congenital anomalies prenatally has improved rapidly, with increased utilization of newer techniques for maternal α-fetoprotein screening, high-resolution ultrasonography, and amniocentesis. Since the early 1990s, it has been possible to prenatally diagnose anencephaly.13,36 In 1994, the Canadian College of Medical Geneticists and the Society of Obstetricians and Gynaecologists of Canada recommended that all women be offered maternal serum α-fetoprotein screening in conjunction with high-resolution ultrasonographic examination and genetic counseling.14 In a previous study,12 we showed that the fetal death rate due to congenital anomalies (a variety of types of anomaly) at 20 to 25 weeks’ gestation doubled, from 18.4 per 100000 fetuses in 1985-1987 to 43.4 per 100000 fetuses in 1994-1996, while rates of fetal death due to congenital anomalies at later gestations and of infant mortality due to congenital anomalies decreased substantially. We have also shown previously12,18 that the pattern of decrease in infant mortality due to congenital malformations is variable across Canada, with some provinces showing larger declines than others. Differences in access to prenatal diagnosis and pregnancy termination for congenital anomalies are related to decreases in overall infant mortality at the population level. Further declines in infant deaths due to congenital anomalies are likely to occur as prenatal diagnosis and selective termination of affected pregnancies become more widely available.


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