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Neonatal morbidity associated with late preterm and early term birth: the roles of gestational age and biological determinants of preterm birth

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Background The aim of this study was to elucidate the role of gestational age in determining the risk of neonatal morbidity among infants born late preterm (34–36 weeks) and early term (37–38 weeks) compared with those born full term (39–41 weeks) by examining the contribution of gestational age within the context of biological determinants of preterm birth.

Methods This was a retrospective cohort study. The sample included singleton live births with no major congenital anomalies, delivered at 34–41 weeks of gestation to London-Middlesex (Canada) mothers in 2002–11. Data from a city-wide perinatal database were linked with discharge abstract data. Multivariable models used modified Poisson regression to directly estimate adjusted relative risks (aRRs). The roles of gestational age and biological determinants of preterm birth were further examined using mediation and moderation analyses.

Results Compared with infants born full term, infants born late preterm and early term were at increased risk for neonatal intensive care unit triage/admission [late preterm aRR = 6.14, 95% confidence interval (CI) 5.63, 6.71; early term aRR = 1.54, 95% CI 1.41, 1.68] and neonatal respiratory morbidity (late preterm aRR = 6.16, 95% CI 5.39, 7.03; early term aRR = 1.46, 95% CI 1.29, 1.65). The effect of gestational age was partially explained by biological determinants of preterm birth acting through gestational age. Moreover, placental ischaemia and other hypoxia exacerbated the effect of gestational age on poor outcomes.

Conclusions Poor outcomes among infants born late preterm and early term are not only due to physiological immaturity but also to biological determinants of preterm birth acting through and with gestational age to produce poor outcomes.

Keywords Preterm birth, pregnancy complications, neonatal intensive care, neonatal respiratory distress syndrome

Introduction

Preterm birth is defined as delivery prior to 37 weeks of gestation. Although infants born toward the end of this preterm period were traditionally assumed to be 'low risk,' recent research has shown increased risk for neonatal morbidity and mortality associated with late preterm birth (34–36 weeks) and early term birth (37–38 weeks). However, it is unclear to what extent these risks are associated directly with being born early or with the reasons for preterm birth.

Compared with term infants, infants born late preterm are at increased risk for neonatal intensive care unit (NICU) admission,[1,2] hospital readmission[2–4] and longer hospital stay.[5] They are also at greater risk for respiratory morbidities,[1,3,5,6] temperature instability,[5,6] hypoglycaemia,[5,6] sepsis,[1,2] hyperbilirubinaemia,[3,5,6] necrotizing enterocolitis,[2] neurological morbidities,[1,2] and even neonatal and infant mortality.[7] Typically, the comparison group for infants born late preterm is those born at 37 weeks of gestation or later. However, research has shown that the median gestational age is 39 weeks.[8] Moreover, infants born at 37 and 38 weeks are at increased risk, compared with their full term peers (39–41 weeks), for NICU admission,[9] hospital readmission[10] and longer stay;[9,10] respiratory[9] and other[9,11,12] neonatal morbidities; and mortality.[13] Whereas some studies have failed to find increased risk at 38 weeks,[9,14] the majority of the literature points to the need to examine early term infants as a separate group.[15]

Although there is evidence for physiological immaturity in the late preterm and early term periods,[16] it is possible that poor outcomes among infants born late preterm and early term are associated not only with being born early but also with the reasons for being born early.[17] Moreover, *in utero* exposure to these pathological conditions associated with early delivery may even exacerbate the risk of poor outcomes.[18] Previous studies have attempted to address this by examining differences among medically indicated and spontaneous preterm deliveries.[19,20] However, this distinction has limited aetiological significance because maternal medical conditions are observed not only in medically indicated preterm birth but also in spontaneous preterm birth.[21] The onset of labour (i.e. physician-initiated or spontaneous) should be considered separately from the presence of maternal medical conditions which contribute to a pathological intrauterine environment regardless of the nature of labour onset. Only a handful of studies have examined the impact of specific maternal medical conditions on neonatal outcomes among infants born late preterm and early term.[22] These 'biological determinants of preterm birth' can be categorized as infection and inflammation, placental ischaemia and other hypoxia, endocrine triggers and other biological determinants[23,24] (see Figure 1).

Objectives

The overall aim of this study was to elucidate the role that gestational age plays in determining risk of neonatal morbidity among infants born late preterm and early term compared with those born full term by examining the contribution of gestational age within the context of biological determinants of preterm birth. The research questions were as follows:

(i) How does the risk of poor neonatal outcomes among infants born late preterm and early term compare with that of infants born full term?
(ii) Does gestational age act as a partial mediator between biological determinants of preterm birth and poor neonatal outcomes?
(iii) Do biological determinants of preterm birth modify the effect of gestational age on poor neonatal outcomes?

Methods

Study design and setting

This retrospective cohort study was conducted in London, Canada. Ethics approval was obtained from the University of Western Ontario Health Sciences

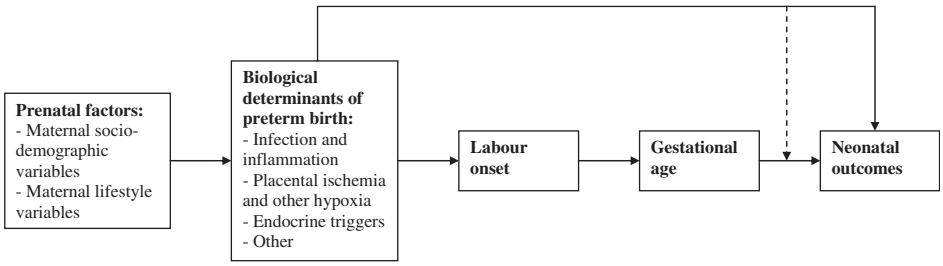

Figure 1 Study conceptual model

Research Ethics Board and from the Lawson Health Research Institute Research Office. Two administrative data sources, a city-wide perinatal database and the hospitals' discharge abstract database, were used. These databases collect information on all births occurring at two teaching hospitals (a level II hospital and a level III hospital) which together service the needs of a population of approximately 360 000 local residents with over 5000 births annually. The study period covered births between 1 April 2002 and 31 March 2011, affording a sample size of 38 807 births after exclusions.

The data sources were linked using infant chart number. The accuracy of this linkage was assessed by comparing variables available in both data sources. If there were discrepancies, the infant was excluded from the analysis according to a set of predetermined rules (see Figure 2).

Participants

Several criteria were used to define the study population: (i) resident of the City of London or Middlesex County, Canada, (because high risk transfers from outside the region to the level III centre have unique risks for maternal and/or neonatal morbidity); (ii) born at 34–41 weeks of gestation (because risks associated with very preterm birth are well established, and post-term deliveries have higher risk for morbidity and mortality than full term deliveries[25]); and (iii) singleton gestation (because twins and higher order multiples have differential risks for early delivery[26] and poor outcomes[27]).

After formulation of the study population, two exclusion criteria were applied to derive the study sample. First, infants with major congenital anomalies were excluded, since major congenital anomalies are associated with both earlier gestational age and with morbidity and mortality.[7] (Major congenital anomalies were defined as life-threatening, disabling or requiring major surgery, including chromosomal trisomies.) Second, stillbirths and neonatal deaths were excluded (refer to the Limitations section for a discussion of this decision).

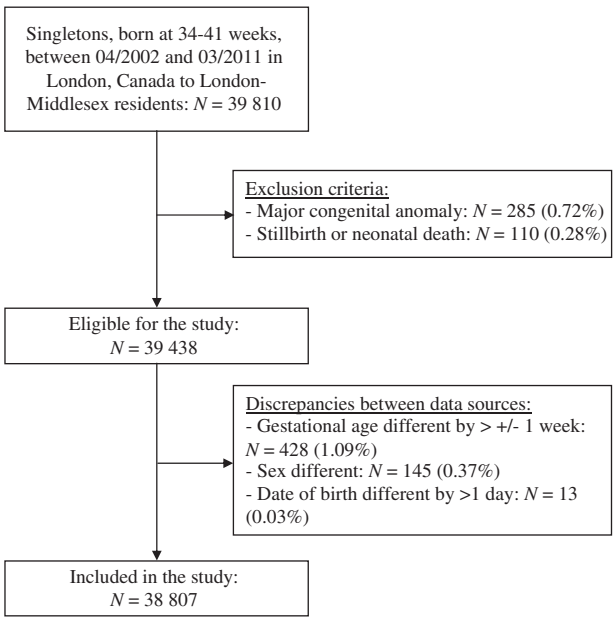

Figure 2 Study flow chart

Data sources

The perinatal database contains information on mothers' socio-demographic characteristics, health during pregnancy and basic neonatal outcomes. Data for all deliveries of infants $\geqslant$20 weeks of gestation or $\geqslant$500 g birthweight[28] were abstracted from medical records and entered into the database. A comprehensive coding manual, with definitions consistent with the International Classification of Disease (ICD), guides the coding and recording of all information. The data arise from clinical activity and are primarily used for clinical audits and research; recording health information in the database is therefore part of hospital protocol. The database was established over 30 years ago and is managed by a team with extensive data collection and management experience.

The discharge abstract database contains diagnostic information on a primary and secondary diagnosis as well as up to 23 additional diagnoses for all infants. Diagnoses are recorded using ICD-10 codes.[29] The database was constructed to enable submission of standardized clinical and administrative information on inpatient discharges to the Canadian Institute for Health Information (CIHI). Data are put through a series of coding quality checks prior to being sent to CIHI.[30]

Measures

Gestational age was based on best obstetric estimate, as recorded in the perinatal database, using the mother's last menstrual period and first trimester ultrasound. The last menstrual period estimate was used if a first trimester ultrasound estimate was within 4 days of the expected date of delivery; otherwise, the ultrasound estimate was used. (In Canada, very few women do not have a prenatal ultrasound. The first ultrasound is, on average, at 14 weeks of gestation, and 66.8% of women receive their first ultrasound prior to 18 weeks.[31]) Gestational age was based on completed weeks [i.e. birth at 36 6/7 weeks (259 days) = gestational age of 36 completed weeks].[32] Infants were classified as late preterm (34–36 weeks of gestation), early term (37–38 weeks) or full term (39–41 weeks), consistent with U.S. National Institute of Child Health and Human Development definitions.[32]

Two outcomes were assessed: NICU triage/admission and neonatal respiratory morbidity. NICU triage/admission was determined from the perinatal database and was used to reflect the overall burden of morbidity

necessitating specialized care. Infants who were triaged were those who were evaluated for NICU admission for a serious morbidity but were not admitted. Triage was included in this outcome definition because it was expected that this would capture morbidities that did not meet the criteria for admission but that were important enough to warrant special attention. At the time of data collection, only the level III centre had NICU facilities. At the level II centre, infants requiring specialized care were admitted to the specialized nursery; for these analyses, this was also considered 'NICU triage/admission.' Information on neonatal respiratory morbidity was obtained from ICD-10 codes[29] in the discharge abstract database and included codes P22.0, P22.1, P22.8, P22.9, P27.1 and P29.3 (i.e. respiratory distress syndrome, transient tachypnoea of the newborn, other respiratory distress of the newborn, respiratory distress of the newborn unspecified, bronchopulmonary dysplasia and persistent pulmonary hypertension, respectively).

Biological determinants of preterm birth were categorized based on definitions used in the previous literature[23,24] and included: infection and inflammation (i.e. bacterial vaginosis, chorioamnionitis, other intrauterine or systemic infections, premature rupture of the membranes), placental ischaemia and other hypoxia [i.e. preeclampsia, eclampsia, gestational and chronic hypertension, small for gestational age (<5th percentile), placenta praevia, placental abruption, other bleeding at >20 weeks of gestation, vascular disease] and other biological determinants (i.e. gestational and pre-existing diabetes mellitus, polyhydramnios, oligohydramnios). Each mother was coded according to whether or not she had one or more of the conditions within each category of the biological determinants of preterm birth. In the perinatal database, depression and anxiety are noted on the basis of medication use and not diagnosis. Therefore, endocrine triggers were not included in this analysis because it was impossible to disentangle the effects of depression and anxiety from those of the medications used to treat them.[33]

Several variables were assessed for their roles as confounders. Potential confounders were selected based on the literature review and on the causal thinking used in the conceptual model. Information on all confounders was obtained from the perinatal database. These variables included prenatal socio-demographic and lifestyle variables (i.e. maternal age, maternal marital status, median neighbourhood family income, parity, previous preterm delivery, previous spontaneous or induced abortion, prenatal care, smoking during pregnancy, drug use during pregnancy, alcohol use during pregnancy); other maternal medical conditions thought to present a risk to the pregnancy (i.e. anaemia, autoimmune conditions, connective tissue disorders, hormonal disease, gastrointestinal disease, haematological disease, renal disease, respiratory disease); labour variables (i.e. cord complications, forceps, vacuum extraction); and additional covariates (i.e. infant sex). Non-reassuring fetal heart rate, fetal distress and labour onset (i.e. caesarean section without labour, induced labour or spontaneous labour) were not included in the multivariable analyses because they were considered to be on the causal pathway.

Statistical analyses

SAS 9.2[34] was used for all analyses. Descriptive analyses included frequencies and percentages to describe the sample. Univariable modified Poisson regression (using SAS PROC GENMOD)[35] was used to assess unadjusted associations between the covariates and the outcomes of interest prior to multivariable analyses.

To address the first research question, adjusted relative risks were directly estimated using multivariable modified Poisson regression[35] with generalized estimating equations (GEE)[36] to adjust the variance for non-independence due to multiple deliveries to the same mother throughout the study period. Parsimonious models for each outcome were built using blockwise entry of variables according to the following conceptual categories: prenatal socio-demographic and lifestyle variables, biological determinants of preterm birth, other pre-delivery covariates, labour variables, gestational age and additional covariates. To achieve a conservative balance between the dual objectives of eliminating bias and minimizing variance, a liberal significance level of $P < .20$ was used to retain covariates at each step,[37] and confidence intervals were used in the final models to reflect clinical rather than statistical significance (due to the large sample size).[38]

To address the second and third research questions, additional analyses were performed on the final multivariable models produced for the first research question. To address research question two, GEE was used to test the significance of the difference in coefficients between full (with gestational age) and reduced (without gestational age) models using methods described by Schluchter.[39] This difference in coefficients represents the indirect effect of the biological determinants of preterm birth (i.e., 'through' gestational age).[39]

To address research question three, additive interaction was explored by calculating the relative excess risk (RERI) due to interaction ($RERI = RR_{11} - RR_{10} - RR_{01} + 1$).[40] Confidence intervals were calculated using the MOVER (method of variance estimates recovery) technique.[40] (Note that for RERIs, 0 indicates no excess risk.)

Results

Infants born between 1 April 2002 and 31 March 2011 (N = 39 438) were eligible for the study. Of these, 631 (1.6%) were excluded due to discrepancies between the two data sources following linkage. This left a sample of 38 807 infants (see Figure 2). Table 1 summarizes the

Table 1 Sample characteristics (N = 38 807)

	N/total	%
Prenatal socio-demographic and lifestyle variables		
Maternal age		
<20 years	1935/38 796	4.99
20-34 years	30 332/38 796	78.18
⩾35 years	6529/38 796	16.83
Maternal marital status		
Single (never married)	5677/38 135	14.89
Widowed, separated, divorced	468/38 135	1.23
Common-law	5971/38 135	15.66
Married	26 019/38 135	68.23
Median neighbourhood family income[a]		
$50,000-$59,999	8797/38 807	23.14
$60,000-$69,999	15 174/38 807	39.10
$70,000-$79,999	6174/38 807	15.91
$80,000-$89,999	5863/38 807	15.11
$90,000 or more	2617/38 807	6.74
Parity		
Nulliparous	17 184/38 807	44.28
Primi/multiparous	21 623/38 807	55.72
Previous preterm delivery		
Yes	2073/38 807	5.34
No	36 734/38 807	94.66
Previous abortion (spontaneous, induced)		
Yes	12 415/38 806	31.99
No	26 391/38 806	68.01
Prenatal care		
None/inadequate (<4 visits at 36 weeks)	558/38 807	1.44
Normal/adequate	38 249/38 807	98.56
Smoking during pregnancy		
Yes	6492/38 806	16.73
No	32 314/38 806	83.27
Drug use during pregnancy		
Yes	949/38 806	2.45
No	37 857/38 806	97.55
Alcohol during pregnancy		
Yes	622/38 804	1.60
No	38 182/38 804	98.40
Biological determinants of preterm birth		
Infection and inflammation		
Yes	2811/38 807	7.24
No	35 996/38 807	92.76
Placental ischaemia and other hypoxia		
Yes	8098/38 807	20.87
No	30 709/38 807	79.13
Other biological determinants		
Yes	3116/38 807	8.03
No	35 691/38 807	91.97
Other pre-delivery covariates		
Other maternal medical conditions		
Yes	8871/38 807	22.86
No	29 936/38 807	77.41
Labour variables		
Cord complications		
Yes	12 073/38 807	31.11
No	26 734/38 807	68.89
Non-reassuring fetal heart rate		
Yes	5976/38 803	15.40
No	32 827/38 803	84.60
Fetal distress		
Yes	791/38 792	2.04
No	38 001/38 792	97.96
Labour onset		
No labour	3369/38 805	8.68
Induced labour	14 343/38 805	36.96
Spontaneous labour	21 093/38 805	54.36
Forceps		
Yes	2932/38 723	7.57
No	35 791/38 723	92.43
Vacuum extraction		
Yes	394/38 803	1.02
No	38 409/38 803	98.98
Gestational age		
Gestational age		
Late preterm	1838/38 807	4.74
Early term	9606/38 807	24.75
Full term	27 363/38 807	70.51
Other covariates		
Infant sex		
Male	19 856/38 807	51.17
Female	18 951/38 807	48.83

[a]Currency of median neighbourhood family income in Canadian dollars.

descriptive statistics for the sample. In the sample, 4.74% of deliveries were late preterm, 24.75% were early term and 70.51% were full term.

Research question one

The overall rate of NICU triage/admission was 6.86% (38.89% in late preterm, 7.68% in early term and 4.56% in full term infants). After controlling for confounders, infants born late preterm (aRR = 6.14, 95% CI 5.63, 6.71) and early term (aRR = 1.54, 95% CI 1.41, 1.68) were at increased risk for NICU triage/admission compared with those born full term (see Table 2).

The overall rate of neonatal respiratory morbidity was 3.52% (17.68% in late preterm, 3.76% in early term and 2.49% in full term infants). After controlling for confounders, infants born late preterm (aRR = 6.16, 95% CI 5.39, 7.03) and early term (aRR = 1.46, 95% CI 1.29, 1.65) were at increased risk for neonatal respiratory morbidity (see Table 3).

Research question two

Gestational age was tested as a partial mediator between the biological determinants of preterm birth and neonatal outcomes. For each outcome, the total, direct and indirect effects of each biological determinant are shown in Table 4. For both NICU triage/admission and neonatal respiratory morbidity, late preterm and early term birth partially mediated the effects of infection and inflammation, placental ischaemia and other hypoxia, and other biological determinants of preterm birth on neonatal outcomes.

Research question three

Next, additive interactions between gestational age and biological determinants of preterm birth were tested (see Table 5). For NICU triage/admission, there was no interaction between infection and inflammation and gestational age. There was evidence of excess risk due to interaction for placental ischaemia and other hypoxia and late preterm birth as well as early term birth. Similar results were seen for other biological determinants of preterm birth and early term birth. For neonatal respiratory morbidity, there was evidence of excess risk due to interaction for only placental ischaemia and other hypoxia and early term birth.

Sensitivity analyses

The relative risks for the biological determinants of preterm birth and gestational age were only slightly attenuated when fetal distress, non-reassuring fetal heart rate and labour onset (pathway variables) were added to the multivariable models (data not shown).

Discussion

These findings show that, consistent with previous research, among infants born late preterm and early term there is elevated risk for NICU triage/admission[1,2,9] and neonatal respiratory morbidity.[1,3,5,6,9] These findings add to a growing body of literature showing that delivery prior to 39 weeks of gestation is associated with poor neonatal outcomes.

A unique finding is that this study shows how and when poor outcomes occur in this late preterm and early term population. The mediation analysis showed that a pathological intrauterine environment (characterized by infection and inflammation, placental ischaemia and other hypoxia, or other biological determinants) acts through early delivery to produce poor outcomes. In other words, gestational age is on the causal path between biological determinants of preterm birth and neonatal outcomes. The moderation analysis adds to this by showing that infants who are exposed to both pathological intrauterine conditions and early delivery have excess risk for poor neonatal outcomes. Previous studies have acknowledged that factors leading to early delivery could influence the effects of mild prematurity on neonatal outcomes.[19,20] However, the majority of these studies have fallen short of addressing this hypothesis by only examining whether deliveries were medically indicated or spontaneous. By examining the roles of gestational age and groups of biological determinants of preterm birth that share a common pathophysiology, this study provides insight into the 'upstream' aetiology of morbidity associated with late preterm and early term birth. The association between infection and inflammation and poor neonatal outcomes may be explained by the ability of pro-inflammatory cytokines to produce a 'fetal inflammatory response'.[41] Placental ischaemia and other hypoxia are characterized by impairment of placental bloodflow which results in reduced delivery of oxygen and nutrients.[42] The mechanisms associated with other biological determinants of preterm birth are less understood; for diabetes, fetal hyperglycaemia and hypoxia may play a role.[43]

Moderated mediation (i.e. when a mediator also interacts with the exposure) has been the subject of a considerable amount of theoretical research.[44–47] Although there is debate surrounding how to test this phenomenon (i.e. in separate analyses[46] as in this paper, or in a complex, combined analysis[45,47]), the results of the mediation and moderation analyses in the current study allow one consistent conclusion to be made: the issue of late preterm and early term birth cannot be considered in isolation. One must also consider the reasons for early delivery, which may act through and with gestational age to produce poor neonatal outcomes.

Strengths and limitations

A major strength of this study was the ability to link two city-wide administrative data sources. Together, these data sources provided rich and detailed information on pregnancy, labour and delivery (perinatal

Table 2 Unadjusted and adjusted associations between covariates and NICU triage/admission

	% triaged or admitted	Unadjusted RR (95% CI)	Unadjusted *P*-value	Adjusted RR (95% CI)	Adjusted *P*-value
Prenatal socio-demographic and lifestyle variables					
Maternal age					
<20 years	7.96	1.20 (1.02, 1.40)	.0149	0.91 (0.77, 1.07)	.2505
20-34 years	6.66	reference		reference	
⩾35 years	7.50	1.13 (1.02, 1.24)	.0271	1.12 (1.02, 1.24)	.0162
Maternal marital status					
Single (never married)	8.77	1.38 (1.25, 1.52)	<.0001	—	
Widowed, separated, divorced	7.69	1.21 (0.86, 1.69)	.0263		
Common-law	7.17	1.12 (1.01, 1.25)	.2716		
Married	6.38	reference			
Median neighbourhood family income					
$50,000-$59,999	7.60	1.14 (0.97, 1.33)	.1218	—	
$60,000-$69,999	6.90	1.03 (0.88, 1.21)	.6930		
$70,000-$79,999	6.54	0.98 (0.82, 1.16)	.8056		
$80,000-$89,999	6.07	0.91 (0.76, 1.08)	.2817		
$90,000 or more	6.69	reference			
Parity					
Nulliparous	8.14	1.39 (1.29, 1.50)	<.0001	1.31 (1.22, 1.42)	<.0001
Primi/multiparous	5.85	reference		reference	
Previous preterm delivery					
Yes	9.74	1.45 (1.27, 1.67)	<.0001	—	
No	6.70	reference			
Previous abortion (induced, spontaneous)					
Yes	6.95	1.02 (0.94, 1.10)	.6394	—	
No	6.82	reference			
Prenatal care					
None/inadequate	19.18	2.87 (2.40, 3.43)	<.0001	1.59 (1.31, 1.93)	<.0001
Normal/adequate	6.69	reference		reference	
Smoking during pregnancy					
Yes	9.10	1.42 (1.30, 1.55)	<.0001	1.07 (0.97, 1.18)	.1530
No	6.42	reference		reference	
Drug use during pregnancy					
Yes	22.02	3.40 (2.99, 3.86)	<.0001	2.12 (1.82, 2.48)	<.0001
No	6.48	reference		reference	
Alcohol during pregnancy					
Yes	11.41	1.68 (1.35, 2.10)	<.0001	—	
No	6.79	reference			

(continued)

Table 2 Continued

	% triaged or admitted	Unadjusted RR (95% CI)	Unadjusted *P*-value	Adjusted RR (95% CI)	Adjusted *P*-value
Biological determinants of preterm birth					
Infection and inflammation					
Yes	16.12	2.62 (2.39, 2.88)	<.0001	1.90 (1.72, 2.09)	<.0001
No	6.14	reference		reference	
Placental ischaemia and other hypoxia					
Yes	11.45	2.02 (1.87, 2.19)	<.0001	1.50 (1.39, 1.62)	<.0001
No	5.66	reference		reference	
Other biological determinants					
Yes	12.68	1.99 (1.80, 2.21)	<.0001	1.47 (1.33, 1.62)	<.0001
No	6.36	reference		reference	
Other pre-delivery covariates					
Other maternal medical conditions					
Yes	8.15	1.26 (1.16, 1.37)	<.0001	1.08 (0.99, 1.17)	.0711
No	6.48	reference		reference	
Labour variables					
Cord complications					
Yes	7.45	1.13 (1.04, 1.22)	.0024	1.09 (1.01, 1.17)	.0299
No	6.60	reference		reference	
Forceps					
Yes	8.02	1.19 (1.04, 1.35)	.0090	—	
No	6.76	reference			
Vacuum extraction					
Yes	10.66	1.56 (1.17, 2.08)	.0025	1.54 (1.14, 2.07)	.0046
No	6.83	reference		reference	
Gestational age					
Gestational age					
Late preterm	38.89	8.09 (7.46, 8.77)	<.0001	6.14 (5.63, 6.71)	<.0001
Early term	7.68	1.68 (1.54, 1.84)	<.0001	1.54 (1.41, 1.68)	<.0001
Full term	4.56	reference		reference	
Other covariates					
Infant sex					
Male	7.91	1.37 (1.27, 1.48)	<.0001	1.31 (1.22, 1.41)	<.0001
Female	5.77	reference		reference	

— = Variable eliminated during model building process.

database) and on neonatal outcomes (discharge abstract database). Utilization of these data sources also enabled us to capture information on all hospital births in London, Canada, during the study period, thus ensuring the generalizability of results to the study population. Moreover, the large sample size allowed for an examination of interactions between gestational age and sometimes uncommon biological determinants of preterm birth.

There are several limitations which should be taken into account. As described by Iams[48] in his recent editorial, our study was subject to issues that characterize all retrospective studies, including potential data inaccuracy and unavailability of all desired

Table 3 Unadjusted and adjusted associations between covariates and neonatal respiratory morbidity

	% with resp. morbidity	Unadjusted RR (95% CI)	Unadjusted *P*-values	Adjusted RR (95% CI)	Adjusted *P*-values
Prenatal socio-demographic and lifestyle variables					
Maternal age					
<20 years	3.72	1.06 (0.84, 1.34)	.6379	—	
20-34 years	3.52	reference			
⩾35 years	3.49	0.99 (0.86, 1.14)	.9191		
Maternal marital status					
Single (never married)	4.44	1.36 (1.18, 1.56)	<.0001	1.15 (1.00, 1.33)	.0756
Widowed, separated, divorced	2.78	0.85 (0.49, 1.46)	.5505	0.82 (0.48, 1.40)	.4638
Common-law	3.95	1.21 (1.05, 1.39)	.0098	1.14 (0.99, 1.31)	.0534
Married	3.27	reference		reference	
Median neighbourhood family income					
$50,000-$59,999	3.99	1.20 (0.95, 1.51)	.1226	—	
$60,000-$69,999	3.59	1.08 (0.86, 1.35)	.4976		
$70,000-$79,999	3.34	1.00 (0.78, 1.29)	.9769		
$80,000-$89,999	2.92	0.88 (0.68, 1.13)	.3151		
$90,000 or more	3.32	reference			
Parity					
Nulliparous	3.88	1.20 (1.08, 1.33)	.0008	1.12 (1.01, 1.25)	.0255
Primi/multiparous	3.24	reference		reference	
Previous preterm delivery					
Yes	5.64	1.66 (1.38, 1.99)	<.0001	—	
No	3.40	reference			
Previous abortion (induced, spontaneous)					
Yes	3.52	1.00 (0.89, 1.12)	.9992	—	
No	3.52	reference			
Prenatal care					
None/inadequate	7.53	2.17 (1.62, 2.91)	<.0001	1.54 (1.12, 2.12)	.0081
Normal/adequate	3.46	reference		reference	
Smoking during pregnancy					
Yes	3.93	1.14 (1.00, 1.31)	.0536	—	
No	3.44	reference			
Drug use during pregnancy					
Yes	6.53	1.90 (1.48, 2.43)	<.0001	1.33 (1.01, 1.74)	.0402
No	3.45	reference		reference	
Alcohol during pregnancy					
Yes	3.70	1.05 (0.70, 1.57)	.8114	0.68 (0.45, 1.04)	.0734
No	3.52	reference		reference	

(continued)

Table 3 Continued

	% with resp. morbidity	Unadjusted RR (95% CI)	Unadjusted *P*-values	Adjusted RR (95% CI)	Adjusted *P*-values
Biological determinants of preterm birth					
Infection and inflammation					
Yes	6.30	1.90 (1.63, 2.22)	<.0001	1.50 (1.29, 1.75)	<.0001
No	3.31	reference		reference	
Placental ischaemia and other hypoxia					
Yes	4.73	1.48 (1.31, 1.66)	<.0001	1.16 (1.04, 1.31)	.0106
No	3.20	reference		reference	
Other biological determinants					
Yes	5.26	1.56 (1.33, 1.83)	<.0001	1.25 (1.07, 1.47)	.0051
No	3.37	reference		reference	
Other pre-delivery covariates					
Other maternal medical conditions					
Yes	3.95	1.16 (1.03, 1.31)	.0143	—	
No	3.40	reference			
Labour variables					
Cord complications					
Yes	3.61	1.04 (0.93, 1.16)	.5237	—	
No	3.48	reference			
Forceps					
Yes	3.82	1.10 (0.91, 1.33)	.3420	—	
No	3.48	reference			
Vacuum extraction					
Yes	3.81	1.08 (0.66, 1.78)	.7582	—	
No	3.52	reference			
Gestational age					
Gestational age					
Late preterm	17.68	7.10 (6.27, 8.05)	<.0001	6.16 (5.39, 7.03)	<.0001
Early term	3.76	1.51 (1.33, 1.71)	<.0001	1.46 (1.29, 1.65)	<.0001
Full term	2.49	reference		reference	
Other covariates					
Infant sex					
Male	4.30	1.59 (1.43, 1.77)	<.0001	1.52 (1.37, 1.69)	<.0001
Female	2.71	reference		reference	

— = Variable eliminated during model building process.

variables. For example, there may have been underestimation of neonatal morbidity due to (for NICU triage/admission) treatment of mild morbidities (e.g. hyperbilirubinaemia) in the well-baby nursery or (for neonatal respiratory morbidity) under-documentation of diagnoses in the discharge abstract database.[49] Certain covariates (e.g. cord complications) may have been overestimated. We were also unable to completely address the conceptual model owing to inadequate information on endocrine triggers. Study-specific prospective collection of data immediately following events of interest would reduce the occurrence of inaccurate data and would ensure collection of all variables needed to address the conceptual model.

Also described by Iams,[48] our study was limited by the measurement of gestational age and the

Table 4 Assessment of partial mediation of biological determinants of preterm birth by gestational age

Mediated relationship	Values on the logarithmic scale			Indirect effect aRR (95% CI)	% of effect explained by gestational age
	Total effect aβ (95% CI)	Direct effect aβ (95% CI)	Indirect effect[a] aβ (95% CI)		
NICU triage/admission[b]					
Infection and inflammation	0.79 (0.69, 0.88)	0.64 (0.55, 0.74)	0.15 (0.10, 0.19)	1.16 (1.11, 1.21)	18.57
Placental ischaemia and other hypoxia	0.59 (0.51, 0.66)	0.41 (0.33, 0.49)	0.18 (0.15, 0.21)	1.19 (1.16, 1.23)	30.19
Other biological determinants of preterm birth	0.58 (0.47, 0.68)	0.39 (0.29, 0.49)	0.19 (0.15, 0.23)	1.21 (1.16, 1.26)	32.99
Neonatal respiratory morbidity[c]					
Infection and inflammation	0.56 (0.41, 0.72)	0.41 (0.25, 0.56)	0.15 (0.11, 0.20)	1.16 (1.12, 1.23)	26.64
Placental ischaemia and other hypoxia	0.34 (0.22, 0.46)	0.15 (0.04, 0.27)	0.19 (0.16, 0.22)	1.21 (1.17, 1.25)	54.35
Other biological determinants of preterm birth	0.41 (0.25, 0.57)	0.23 (0.07, 0.39)	0.18 (0.14, 0.22)	1.20 (1.15, 1.25)	45.52

[a]Indirect = total effect − direct effect; indirect effect is equal to G*variable interaction in GEE model assessing mediation.[39]
[b]Controls for maternal age, parity, prenatal care, smoking during pregnancy, drug use during pregnancy, maternal medical conditions, cord complications, vacuum extraction and infant sex.
[c]Controls for maternal marital status, parity, prenatal care, drug use during pregnancy, alcohol use during pregnancy and infant sex.

Table 5 Assessment of additive interaction between biological determinants of preterm birth and gestational age

Interaction	aRERI (95% CI)[a]
NICU triage/admission[b]	
Infection and inflammation	
and late preterm birth	−0.07 (−1.68, 1.92)
and early term birth	−0.55 (−1.10, 0.65)
Placental ischaemia and other hypoxia	
and late preterm birth	2.89 (1.78, 4.08)
and early term birth	0.80 (0.45, 1.16)
Other biological determinants of preterm birth	
and late preterm birth	−0.04 (−1.11, 1.16)
and early term birth	0.44 (0.04, 0.87)
Neonatal respiratory morbidity[c]	
Infection and inflammation	
and late preterm birth	−0.27 (−2.08, 1.92)
and early term birth	−0.30 (−1.03, 0.55)
Placental ischaemia and other hypoxia	
and late preterm birth	0.90 (−0.54, 2.44)
and early term birth	0.48 (0.07, 0.92)
Other biological determinants of preterm birth	
and late preterm birth	1.58 (−0.36, 4.01)
and early term birth	0.17 (−0.42, 0.79)

[a]Relative excess risk due to interaction: $RERI = RR_{11} - RR_{10} - RR_{01} + 1$ (null value = 0).[40]
[b]Controls for maternal age, parity, prenatal care, smoking during pregnancy, drug use during pregnancy, maternal medical conditions, cord complications, vacuum extraction and infant sex, as well as the main effects for gestational age and biological determinants of preterm birth.
[c]Controls for maternal marital status, parity, prenatal care, drug use during pregnancy, alcohol use during pregnancy and infant sex, as well as the main effects for gestational age and biological determinants of preterm birth.

assumptions behind its interpretation. There may have been non-differential misclassification of gestational age due to 'mixing' of adjacent categories (late preterm/early term or early term/full term). Moreover, we assume that gestational age is an accurate marker of fetal maturity. This may be a limitation if different fetuses have different levels of functional maturity at a given gestational age. Improvement of measurement of fetal maturity would make findings in future studies more robust.

It should be noted that the exclusion of stillbirths and neonatal deaths from the study sample restricts the scope of the conclusions; the magnitude of the risks found for the investigated associations is only applicable to survivors. Stillbirths were excluded since the goal of the study was to examine the impacts of both prematurity and the biological

determinants of preterm birth. Stillbirth, by definition, is not a possible consequence of prematurity.[50] Both stillbirths and neonatal deaths were extremely rare in the study population. Any bias resulting from their exclusion would likely be in the direction of the null. Results remain useful to clinicians who at these later gestational ages will be mainly concerned with risks of morbidity among survivors.

Future research and implications

Future research could build upon this study by further refining the measurement of biological determinants of preterm birth through re-examination of the model using a dataset with diagnostic information on endocrine triggers and through re-grouping of 'other biological determinants' as understanding of the pathophysiology of these conditions improves. Moreover, the inter-relationship between gestational age and biological determinants of preterm birth could be investigated in relation to other outcomes of importance to late preterm and early term birth (e.g. hypoglycaemia, hyperbilirubinaemia).

A dramatic increase in preterm birth over the past 20 years has received worldwide attention.[51] A rise in the rate of late preterm birth accounts for most of this increase.[52] Moreover, elective deliveries in the early term period are becoming more common.[15] An understanding of the causes of poor outcomes in these infants is therefore critical. The risks of early delivery should be weighed carefully against the risks of prolonging pregnancy. Although gestational age remains a strong predictor of poor neonatal outcomes even during the late preterm and early term periods, this study shows that biological determinants of preterm birth may act through and with gestational age to produce poor neonatal outcomes.

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KEY MESSAGES

- This study found that, compared with infants born full term (at 39–41 weeks of gestation), infants born late preterm (34–36 weeks) and early term (37–38 weeks) were at increased risk for neonatal intensive care unit triage/admission and for neonatal respiratory morbidity.
- The effect of gestational age was partially explained by biological determinants of preterm birth acting through early delivery to produce poor outcomes; these biological determinants of preterm birth also exacerbated the effect of gestational age.
- These findings show that it is important to consider the reasons for early delivery when determining the level of risk associated with late preterm and early term birth.

References

[1] Cheng YW, Kaimal AJ, Bruckner TA, Hallaron DR, Caughey AB. Perinatal morbidity associated with late preterm deliveries compared with deliveries between 37 and 40 weeks of gestation. *BJOG* 2011;**118:**1446–54.

[2] Melamed N, Klinger G, Tenebaum-Gavish K *et al*. Short-term neonatal outcome in low-risk, spontaneous, singleton, late preterm deliveries. *Obstet Gynecol* 2009;**114:** 253–60.

[3] Jaiswal A, Murki S, Gaddam P, Reddy A. Early neonatal morbidities in late preterm infants. *Indian Pediatr* 2010;**20:** 1–5.

[4] Tomashek KM, Shapiro-Mendoza CK, Weiss J *et al*. Early discharge among late preterm and term newborns and risk of neonatal morbidity. *Semin Perinatol* 2006;**30:**61–68.

[5] Leone A, Ersfeld P, Adams M, Meyer Schiffer P, Bucher HU, Arlettaz R. Neonatal morbidity in singleton late preterm infants compared with full-term infants. *Acta Paediatr* 2012;**101:**e6–10.

[6] Bird TM, Bronstein JM, Hall RW, Lowery CL, Nugent R, Mays GP. Late preterm infants: Birth outcomes and health care utilization in the first year. *Pediatrics* 2010; **126:**e311–19.

[7] Tomashek KM, Shapiro-Mendoza CK, Davidoff MJ, Petrini JR. Differences in mortality between late-preterm and term singleton infants in the United States, 1995-2002. *J Pediatr* 2007;**151:**450–56.

[8] Davidoff MJ, Dias T, Damus K *et al*. Changes in the gestational age distribution among U.S. singleton births: Impact on rates of late preterm birth, 1992 to 2002. *Semin Perinatol* 2006;**30:**8–15.

[9] Tita ATN, Landon MB, Spong CY *et al*. Timing of elective repeat cesarean delivery at term and neonatal outcomes. *N Engl J Med* 2009;**360:**111–20.

[10] Dietz PM, Rizzo JH, England LJ *et al*. Early term delivery and health care utilization in the first year of life. *J Pediatr* 2012;**161:**234–39.

[11] McIntire DD, Leveno KL. Neonatal mortality and morbidity rates in late preterm births compared with births at term. *Obstet Gynecol* 2008;**111:**35–41.

[12] Ruth CA, Roos N, Hildes-Ripstein E, Brownell M. The influence of gestational age and socioeconomic status on neonatal outcomes in late preterm and early term

gestation: A population-based study. *BMC Pregnancyd Childbirth* 2012;**12:**62.
[13] Donovan EF, Besl J, Paulson J, Rose B, Iams J. for the Ohio Perinatal Quality Collaborative. Infant death among Ohio resident infants born at 32 to 41 weeks of gestation. *Am J Obstet Gynecol* 2010;**203:**e1–5.
[14] Zhang X, Kramer MS. Variations in mortality and morbidity by gestational age among infants born at term. *J Pediatr* 2009;**154:**358–62.
[15] Engle WA, Kominiarek MA. Late preterm infants, early term infants, and timing of elective deliveries. *J Pediatr* 2009;**35:**325–41.
[16] Raju TNK. Developmental physiology of late and moderate prematurity. *Semin Fetal Neonatal Med* 2012;**17:**126–31.
[17] Wilcox AJ, Weinberg CR, Basso O. On the pitfalls of adjusting for gestational age at birth. *Am J Epidemiol* 2011; **174:**1062–68.
[18] Basso O, Wilcox A. Mortality risk among preterm babies: immaturity versus underlying pathology. *Epidemiology* 2010;**21:**521–27.
[19] Chen A, Feresu SA, Barsoom MJ. Heterogeneity of preterm birth subtypes in relation to neonatal death. *Obstet Gynecol* 2009;**114:**516–22.
[20] Lee J, Seong HS, Jae B, Kwan J, Romero R, Yoon BH. Evidence to support that spontaneous preterm labour is adaptive in nature: neonatal RDS is more common in ''indicated'' than in ''spontaneous'' preterm birth. *J Perinat Med* 2009;**37:**53–58.
[21] Klebanoff MA, Shiono PH. Top down, bottom up, and inside out: reflections on preterm birth. *Paediatr Perinat Epidemiol* 1995;**9:**125–29.
[22] Shapiro-Mendoza CK, Tomashek KM, Kotelchuck M *et al*. Effect of late-preterm birth and maternal medical conditions on newborn morbidity risk. *Pediatrics* 2008;**12:**e223–32.
[23] Lockwood CJ, Kuczynski E. Markers of risk for preterm delivery. *J Perinat Med* 1999;**27:**5–20.
[24] Romero R, Espinoza J, Kusanovic JP *et al*. The preterm parturition syndrome. *BJOG* 2006;**113:**17–42.
[25] Cheng YW, Nicholson JM, Nakagawa S, Bruckner TA, Washington AE, Caughey AB. Perinatal outcomes in low-risk term pregnancies: Do they differ by week of gestation? *Am J Obstet Gynecol* 2008;**199:**370.
[26] Joseph KS, Kramer MS, Marcoux S *et al*. Determinants of preterm birth rates in Canada from 1981 through 1983 and from 1992 through 1994. *N Engl J Med* 1998;**339:** 1434–39.
[27] Payne JC, Campbell MK, DaSilva O, Koval J. Perinatal mortality in term and preterm twin and singleton births. *Twin Res* 2002;**5:**260–64.
[28] Statistics Canada. *Vital Statistics – Stillbirth Database; 2013*. http://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&SDDS=3234&Item_Id=1530&lang=en (23 May 2013, date last accessed).
[29] World Health Organization. *International Classification of Diseases and Related Health Problems, Tenth Revision*. Geneva: World Health Organization, 1992.
[30] Canadian Institute for Health Information. *Data Quality Documentation for External Users: Discharge Abstract Database, 2010-2011*. Ottawa (ON): Canadian Institute for Health Information, 2011.
[31] Public Health Agency of Canada. *What Mothers Say: The Canadian Maternity Experiences Survey*. Ottawa (ON): Public Health Agency of Canada, 2009.
[32] Raju TNK, Higgins RD, Stark AR, Leveno KJ. Optimizing care and outcomes for late-preterm (near-term) infants: A summary of the workshop sponsored by the National Institute of Child Health and Human Development. *Pediatrics* 2006;**118:**1207–14.
[33] Wisner KL, Sit DKY, Hanusa BH *et al*. Major depression and antidepressant treatment: impact on pregnancy and neonatal outcomes. *Am J Psychiatry* 2009;**166:**557–66.
[34] SAS Institute. *SAS/STAT 9.2 User's Guide*. Cary, NC: SAS Institute, 2008.
[35] Zou GY. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004; **159:**702–06.
[36] Zou GY, Donner A. Extension of the modified Poisson regression model to prospective studies with correlated binary data. *Stat Methods Med Res* 2011; 8 Nov. PMID 22072596.
[37] Hoerl RW, Schuenemeyer JH, Hoerl AE. A simulation of biased estimation and subset selection regression techniques. *Technometrics* 1986;**28:**1273–84.
[38] Gardner MJ, Altman DG. Confidence intervals rather than P values: estimation rather than hypothesis testing. *Br Med J (Clin Res Ed)* 1986;**292:**746.
[39] Schluchter MD. Flexible approaches to computing mediated effects in generalized linear models: Generalized estimating equations and bootstrapping. *Multivariate Behav Res* 2008;**43:**268–88.
[40] Zou GY. On the estimation of additive interaction by use of the four-by-two table and beyond. *Am J Epidemiol* 2008;**168:**212–24.
[41] Viscardi RM, Muhumuza CK, Rodriguez A *et al*. Inflammatory markers in intrauterine and fetal blood and cerebrospinal fluid compartments are associated with adverse pulmonary and neurologic outcomes in preterm infants. *Pediatr Res* 2004;**55:**1009–17.
[42] Ananth CV, Vintzileos AM. Maternal-fetal conditions necessitating a medical intervention resulting in preterm birth. *Am J Obstet Gynecol* 2006;**195:**1557–63.
[43] Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in type 1 diabetic pregnancies. *Diabetes Care* 2009;**32:**2005–09.
[44] Preacher KJ, Rucker DD, Hayes AF. Addressing moderated mediation hypotheses: Theory, methods, and prescriptions. *Multivariate Behav Res* 2007;**42:**185–227.
[45] Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. *Epidemiology* 1992;**3:** 143–55.
[46] Judd CM, Kenny DA. Process analysis estimating mediation in treatment evaluations. *Eval Rev* 1981;**5:**602–19.
[47] Valeri L, VanderWeele TJ. Mediation analysis allowing for exposure–mediator interactions and causal interpretation: Theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Methods* 2013;**18:**137–50.
[48] Iams JD. Late preterm birth: more and better data needed. *Am J Obstet Gynecol* 2011;**205:**395.
[49] Joseph K, Fahey J. Validation of perinatal data in the Discharge Abstract Database of the Canadian Institute for Health Information. *Chronic Dis Can* 2009;**29:**96–100.
[50] Caughey AB. Measuring perinatal complications: Methodological issues related to gestational age. *BMC Pregnancy Childbirth* 2007;**7:**18.
[51] Beck S, Wojdyla D, Say L *et al*. The world-wide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull World Health Organ* 2010;**88:**31–38.
[52] March of Dimes. *Global Report on Birth Defects: The Hidden Toll of Dying and Disabled Children*. New York: March of Dimes Foundation, 2006.