Substance Use of Pregnant Women and Early Neonatal Morbidity: Where to Focus Intervention?

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ABSTRACT

Background: Few studies, and none in Canada, have examined the relation between maternal smoking, alcohol consumption and drug dependence during pregnancy and early neonatal morbidity.

Methods: We analyzed records of singleton live births in Alberta, Canada. Markers of neonatal morbidity were Apgar scores (<7 at 5 minutes postpartum) and resuscitation measures (2001-2005, N=191,686), and neonatal intensive care unit (NICU) admissions (2002-2005, N=154,924). Logistic regression was used to estimate odds ratios (ORs) for self-reported substance use and maternal health before conception, adjusting for maternal age, parity, year and fetal gender. Univariate ORs and population-attributable fractions were computed with and without correction for under-reporting of substance use.

Results: Maternal smoking during pregnancy was the most prevalent risk factor, affecting 20% of mothers by self-report, with the figure being possibly twice as high once corrected for under-reporting. Smoking (ORs 1.2), alcohol consumption (ORs 1.2-1.5) and drug dependence (ORs 1.7-2) by the mother during pregnancy were associated with increased risk for each of the markers of early neonatal morbidity ($p < 0.05$, after correcting for covariates). Eliminating the most common among these risk factors, maternal smoking, would prevent 10-15% of each of the three neonatal morbidity markers. Other recorded factors related to mother's pre-conception health, despite some strong associations, were responsible for only a small proportion of cases.

Discussion: We conclude that in preventing early neonatal morbidity among singleton births in Alberta, control of maternal smoking, the most common of the potentially modifiable risk factors, remains an important goal.

Key words: Pregnancy; epidemiology; neonatology; substance-related disorders; smoking

La traduction du résumé se trouve à la fin de l'article.

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Maternal smoking and use of narcotics are associated with adverse birth outcomes: low birthweight,¹⁻³ prematurity,^{2,3} and that maternal alcohol consumption can lead to Fetal Alcohol Spectrum Disorders,^{4,5} but not restricted fetal growth and prematurity.^{6,7} There has been much less discussion about the impact of substance use on immediate postnatal health of the neonate. For low Apgar score (<7 at 5 minutes), the best-established index of immediate postnatal health,⁸⁻¹⁰ the most extensive data are in relation to smoking; there are also some data on admission to neonatal intensive care units (NICU). A prospective cohort study on 2,000 consecutive patients in Dulwich hospital, London, UK, compared neonatal morbidity between infants of smoking and non-smoking mothers.¹¹ Although the incidence of low Apgar and NICU transfer tended to be higher in infants of smoking mothers, there was no dose-response. A prospective cohort of 110 pregnant women in Netherlands¹² found no relationship between low Apgar scores and NICU transfer with maternal serum carboxyhemoglobin and thiocyanate levels. Kullander et al.¹³ followed 6,376 pregnant women throughout their pregnancy and found no difference in Apgar scores between smoker and non-smoker mothers. On the other hand, a retrospective cohort study of >1 million infants born in Sweden between 1983 and 1997 reported a small increased risk of low Apgar scores in infants born to smoker mothers.^{14,15} This effect appears to be independent of prematurity and birthweight.¹⁵ Bosley et al.¹⁶ observed an elevated incidence of Apgar scores <6 at 1 minute of life in 26,576 singleton infants delivered to smokers in

the Cardiff birth survey of 1970-78. Infants born to mothers who smoked had higher rates of NICU transfer and longer NICU stay.^{11,17} A hospital-based study of 416,834 live births (1998-2002) in Australia indicated that children born to drinking and drug-dependent mothers were more likely to have low Apgar score and be admitted to NICU.^{18,19} A 10-year study of 43,181 deliveries in Croatia found a much higher rate of 5-minute Apgar scores <7 in infants of 85 drug-dependent women.²⁰

Smoking is common in pregnant women in Alberta – occurring in at least one quarter of pregnancies resulting in live births between 1997 and 2000 – and constitutes an important public health issue.²¹ Little is known, however, about the contribution of substance use to the early morbidity of neonates in Alberta, Canada. Consequently, it is difficult to determine with certainty which modifiable risk factors should be the focus of any public health

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Conflict of Interest: None to declare.

Table 1. Frequency of Risk Factors and Measures of Neonatal Morbidity

Risk Factors/Exposures	All Births 2001-2005 (2002-2005)*		Measures of Early Neonatal Morbidity (case)					
	Subjects Exposed	%	Apgar <7 (5 minute)		NICU Admission*		Resuscitation Required	
			Cases Exposed	%†	Cases Exposed	%†	Cases Exposed	%†
Smoking at any time during pregnancy	39,555 (31,141)	20.6 (20.1)						
Alcohol consumption (≥1 drink per day or one occasion of ≥3 drinks)	3768 (3151)	2.0 (2.0)	138	3.6	526	3.1	206	3.1
Drug dependence	2140 (1860)	1.1 (1.2)	90	2.3	404	2.3	152	2.3
Weight <45 kg	996 (830)	0.5 (0.5)	24	0.6	157	0.9	48	0.7
Height <152 cm	3401 (2721)	1.8 (1.8)	83	2.2	419	2.4	119	1.8
Diabetes								
Controlled by diet only	524 (423)	0.3 (0.3)	17	0.4	66	0.4	24	0.4
Controlled by insulin	970 (776)	0.5 (0.5)	44	1.1	243	1.4	43	0.7
With retinopathy	35 (24)	0.02 (0.02)	0	0	10	0.06	2	0.03
Heart disease that affects daily living	170 (146)	0.1 (0.1)	5	0.1	26	0.2	9	0.1
Hypertension								
≥140/90 (pre-pregnancy)	1260 (1008)	0.7 (0.7)	47	1.2	177	1.0	66	1.0
Treated by medication	687 (576)	0.4 (0.4)	32	0.8	131	0.8	34	0.5
Chronic renal disease	189 (153)	0.1 (0.1)	10	0.3	24	0.1	14	0.2
Age ≤25 years	60,322 (48,399)	31.5 (31.2)	1386	35.5	5165	30.0	2468	37.6
Nulliparous	81,889 (66,508)	42.7 (43.0)	2077	53.9	8893	51.6	3751	57.2
Male infant	98,288 (79,349)	51.3 (51.2)	2169	56.3	9620	55.8	3461	52.7

* NICU admission analysis is based on 2002-2005 data only (154,924 births), the other two outcomes are based on 2001-2005 data (191,686 births).

† Percent of cases who were exposed (p_c).

Table 2. Univariate Logistic Regressions and Population-attributable Fractions (PAF) of the Three Measures of Early Neonatal Morbidity

Risk Factors (Dichotomized)	Apgar Score Less Than 7 at 5 Minutes Postpartum			Admission to Neonatal Intensive Care Unit			Postnatal Need of 'Serious' Resuscitation Measures in Neonate		
	OR	95% CI	PAF (%)	OR	95% CI	PAF (%)	OR	95% CI	PAF (%)
Smoking at any time during pregnancy	1.30	1.21-1.40	5.81	1.15	1.11-1.20	2.89	1.30	1.23-1.38	5.80
Alcohol consumption (≥1 drink per day or one occasion of ≥3 drinks)	1.89	1.59-2.24	1.69	1.62	1.47-1.78	1.17	1.65	1.43-1.91	1.24
Drug dependence	2.17	1.75-2.69	1.26	2.25	2.01-2.51	0.56	2.19	1.85-2.58	1.26
Weight <45 kg	1.21	0.80-1.81	0.11	1.87	1.57-2.23	0.42	1.43	1.07-1.92	0.22
Height <152 cm	1.22	0.98-1.53	0.39	1.47	1.32-1.63	0.78	1.02	0.85-1.23	0.04
Diabetes									
Controlled by diet only	1.56	0.95-2.56	0.15	1.48	1.14-1.93	0.12	1.37	0.91-2.07	0.10
Controlled by insulin	2.33	1.72-3.16	0.65	3.68	3.16-4.29	1.03	1.31	0.97-1.78	0.16
With retinopathy	– †			5.76	2.56-12.96	0.05	1.73	0.42-7.15	0.01
Heart disease that affects daily living	1.48	0.61-3.61	0.04	1.74	1.14-2.66	0.06	1.59	0.81-3.10	0.05
Hypertension									
≥140/90 (pre-pregnancy)	1.90	1.42-2.55	0.58	1.71	1.45-2.01	0.43	1.57	1.22-2.00	0.37
Treated by medication	2.39	1.68-3.42	0.48	2.36	1.94-2.87	0.44	1.48	1.04-2.08	0.17
Chronic renal disease	2.73	1.44-5.16	0.16	1.49	0.96-2.30	0.05	2.26	1.31-3.90	0.12
Age ≤25 years	1.20	1.13-1.29	5.92	0.94	0.90-0.97	3.96‡	1.33	1.26-1.40	9.33
Nulliparous*	1.58	1.48-1.69	19.9	1.48	1.43-1.52	16.7	1.84	1.75-1.93	26.1
Male infant*	1.23	1.15-1.31	10.5	1.23	1.19-1.27	10.4	1.06	1.01-1.12	2.98

OR=odds ratio; CI=confidence interval.

* not modifiable risk factors.

† there were no cases of low Apgar among mothers who had diabetes accompanied by retinopathy (35 births).

‡ for maternal age >25 years.

interventions to reduce neonatal morbidity in this province. Our objectives were to determine the contribution of maternal substance use to early neonatal morbidity of live singletons born in Alberta and to estimate the proportion of morbidities that could be prevented by the successful elimination of any one of these risks.

METHODS

We assembled information on all live singleton deliveries in Alberta in 2001-2005 from the delivery records held by the Alberta Perinatal Health Program (APHP). The APHP collects perinatal data from the delivery record for all hospital births and registered midwife-attended home births in the province. Entries with an incomplete delivery record (approximately 2%) with respect to variables of interest were excluded. Substance use measures, obtained during labour but normally prior to birth, were answers to questions about maternal smoking anytime during pregnancy, alcohol consumption (≥1 drink per day or one occasion of ≥3 drinks) and drug dependence. Expectation that this self-reported assessment of risk-related behaviour will have poor sensitivity (unwillingness to admit substance

use) but nearly perfect specificity (no reason to invent substance use)²² is integrated into the statistical analysis. Information on age, year of birth, parity, chronic disease pre-pregnancy health and the gender of the infant was obtained. Early neonatal morbidity was assessed by 1) Apgar score less than 7 at 5 minutes postnatal, 2) transfer of the newborn to NICU, and 3) 'serious' resuscitation (endo-tracheal intubation, positive pressure ventilation, cardio-pulmonary resuscitation). Ethical approval was obtained from the University of Alberta Health Ethics Research Board.

The measures of neonatal morbidity were related to risk factors by logistic regression that estimated odds ratios (OR) and associated 95% confidence limits (CI) (PROC LOGISTIC in SAS 9.1, Cary Institute, NC). Each risk factor was first considered on its own (univariate analysis) and then in combination with all other covariates that were statistically significant in a multivariable model (p<0.05). Univariate analysis was accompanied by calculation of population-attributable fraction (PAF).²³

We investigated the extent to which misclassification due to self-reported substance use affected point estimates of both OR and PAF.

Table 3. Multivariable Logistic Regressions of the Three Measures of Early Neonatal Morbidity

Risk Factors (Dichotomized)	Apgar Score Less Than 7 at 5 minutes Postpartum		Admission to Neonatal Intensive Care Unit		Postnatal Need of 'Serious' Resuscitation Measures in Neonate	
	OR	95% CI	OR	95% CI	OR	95% CI
Smoking at any time during pregnancy	1.23	1.14-1.33	1.17	1.21-1.22	1.23	1.16-1.31
Alcohol consumption (≥ 1 drink per day or one occasion of ≥ 3 drinks)	1.49	1.24-1.79	1.34	1.21-1.48	1.24	1.06-1.44
Drug dependence	1.67	1.33-2.10	2.00	1.77-2.25	1.71	1.43-2.04
Weight <45 kg			1.69	1.42-2.02		
Height <152 cm			1.38	1.24-1.54		
Diabetes						
Controlled by diet only			1.46	1.12-1.90		
Controlled by insulin	2.28	1.68-3.09	3.56	3.05-4.16		
With retinopathy			3.01	1.26-7.18		
Heart disease that affects daily living			1.61	1.04-2.47		
Hypertension						
$\geq 140/90$ (pre-pregnancy)					1.47	1.15-1.89
Treated by medication	2.22	1.54-3.19	2.12	1.73-2.59		
Chronic renal disease	2.26	1.18-4.34			2.15	1.24-3.72
Age ≤ 25 years			0.80	0.77-0.83	1.09	1.03-1.15
Nulliparous	1.59	1.49-1.70	1.54	1.49-1.59	1.80	1.71-1.89
Male infant	1.23	1.15-1.31	1.23	1.20-1.27	1.06	1.01-1.12
Year: 2005 (reference)			1.00	–	1.00	–
2004			0.99	0.95-1.03	0.88	0.82-0.95
2003			0.92	0.88-0.96	0.94	0.87-1.01
2002			0.85	0.81-0.89	0.89	0.83-0.96
2001					0.67	0.62-0.73

Only statistically significant covariates are included; OR = odds ratio; CI = confidence interval.

For self-reported smoking and alcohol consumption, we assumed the sensitivity (*SN*) was 0.5, the same as that for self-reported smoking in this population, determined in a validation study.²² For drug dependence, we assumed a lower sensitivity of 0.25. Specificity (*SP*) of all three self-reported behaviours was fixed at 1. The difference between the true odds ratio (Ψ) and the observed one in presence of non-differential exposure misclassification is characterized by *SN* and *SP* of the exposure classifier and, given the *observed* exposure prevalence p_c and p_o among cases and controls respectively, is calculated according to equation 5.3 in Gustafson:²⁴

$$\Psi = \frac{(p_c + SP - 1) / (SN - p_c)}{(p_o + SP - 1) / (SN - p_o)}$$

Taking into account non-differential exposure misclassification, $PAF = r_c(\Psi - 1) / \Psi$ where r_c is the true proportion of cases exposed, calculated as $r_c = (p_c + SP - 1) / (SP + SN - 1)$.^{24,25}

RESULTS

Apgar scores and resuscitation measures were available for the entire 2001-2005 period (191,686 deliveries), but NICU admissions were consistently recorded only for 2002-2005 (154,924 deliveries). There were not obvious patterns to missingness and the rate of the three outcomes in excluded records (approximately 2%) was not materially different from those retained in analysis. Five-minute Apgar score was less than 7 in 2.01% of singleton births ($n=3,854$), 3.42% of singleton neonates required 'serious' resuscitation measures ($n=6,564$) and 11.13% of singleton neonates were transferred to NICU ($n=17,241$). The three morbidity measures were only weakly correlated (phi correlation²⁶ 0.1-0.2), suggesting that these variables capture different aspects of neonatal morbidity.

Maternal smoking during pregnancy was the most prevalent modifiable risk factor, reported by 22% of mothers of NICU cases and 25% of mothers of low Apgar and "resuscitation" neonates; for alcohol consumption and drug dependence, the proportion of exposed cases was 3.1-3.6 and 2.3%, respectively (Table 1). These proportions would double for smoking and alcohol consumption and quadruple for drug dependence if our estimates of under-reporting are correct.

In univariate analyses, all the considered risk factors tended to be associated with higher risk of early neonatal morbidity (Table 2), except that infants born to mothers greater than 25 years of age were less likely than those born to younger mothers to have low Apgar and be resuscitated, but were more likely to be transferred to NICU. In both univariate (Table 2) and multivariable analyses (Table 3), substance use of the mother during pregnancy was associated with increased risk of early neonatal morbidity, with the relative risk being highest for drug-dependent mothers (elevated by 67-100%) and lowest for mothers who smoked (elevated by about 20%) in the multivariable analysis. Univariate correction for non-differential exposure misclassification increased the ORs shown for substance use in Table 2 (Figure 1).

Smoking during pregnancy, by far the most common among modifiable risk factors (other than mother's age), has the highest PAF: some 6% for low Apgar and resuscitation measures and close to 3% for NICU admission (Table 2). These estimates doubled or even tripled when corrected for under-reporting of substance use (Figure 2). Such correction for under-reporting changed the rank order of PAF of alcohol consumption and drug dependence. Before correction, alcohol consumption appeared to be responsible for 1.7% of low Apgar scores, for example, compared with 1.3% for drug dependence; after correction, alcohol consumption accounted for 3.4% of low Apgar scores, a smaller proportion than that associated with drug dependence (5.2%).

In multivariable analyses (Table 3), male infants were at an elevated risk according to all three markers of neonatal morbidity. Maternal factors independently associated with increased risk of low Apgar were diabetes controlled by insulin, pre-pregnancy hypertension treated by medication, chronic renal disease and nulliparity. The increased risk of NICU admission, after correction for substance use, was independently associated with low maternal weight and height, diabetes, heart disease that affected daily living, pre-pregnancy hypertension treated by medication, older maternal age and nulliparity. The pre-conception factors independently associated with increased risk of the need for 'serious' resuscitation measures were pre-pregnancy hypertension not treat-

Figure 1. Odds ratios (OR) for measures of neonatal morbidity corrected for errors due to self-report of substance use

Note: Non-differential misclassification assumed; sensitivity for smoking and drinking 0.5, for drug dependence 0.25, all specificities are 1.

ed by medication, chronic renal disease, younger maternal age and nulliparity. In addition, there was some trend towards increased admission to NICU and use of resuscitation measures in births that occurred in more recent years.

DISCUSSION

The main findings of this analysis are that smoking, daily or high alcohol consumption and drug dependency during pregnancy contribute to early neonatal morbidity and that eliminating maternal smoking would prevent 10-15% of each of the three markers of neonatal morbidity. Chronic disease was rare and, despite some strong associations, was responsible for only a small proportion of the outcomes.

Our finding of an approximately 20% increase in relative risk with smoking of Apgar score <7 at 5 minutes (before adjustment for misclassification) is in agreement with the estimate from a Swedish cohort of term live births (OR 1.16, 95% CI 1.10-1.24).¹⁵ While Thorngren-Jerneck and Herbst¹⁵ noted that they were unable to correct their estimates for alcohol intake and drug abuse, we demonstrated that maternal smoking acted independently of these risk factors. This is important in light of clustering of substance use.²⁷ Our observation that infants born to smokers were more likely to be admitted to NICU is congruent with report of Miles et al.¹⁷ that such infants, even among drug-dependent mothers, had a longer NICU stay.

The observation that daily or high alcohol consumption during pregnancy is associated with early neonatal morbidity stands in contrast to the synthesis of evidence (of data of similar quality to ours) that suggests little or no adverse effect of even binge drinking on fetal growth and prematurity.^{6,7} A study from Australia¹⁸ reported results on alcohol that were similar to ours. It is possible that maternal alcohol consumption affects early neonatal morbidity independently of common measures of birth complications.⁷

Observations on the effects of drug dependence are complicated by the range of substances in use, the presence of the drug (or its withdrawal) at the time of delivery, increased risk of co-morbidities and, perhaps, preferential admission to high-intensity care for such infants. Although both the Australian¹⁹ and Croatian²⁰ studies report-

Figure 2. Population-attributable fractions (PAF) for measures of neonatal morbidity corrected for errors due to self-report of substance use

Note: Non-differential exposure misclassification assumed; sensitivity for smoking and drinking 0.5, for drug dependence 0.25, all specificities are 1.

ed doubling of risk of low Apgar in drug-addicted mothers, the effect on NICU admission varied strongly with the type of narcotic.¹⁹

The main limitation of the current study is its reliance on self-reported assessment of health-related behaviours that are known to be under-reported by pregnant women, as our own work in Alberta clearly confirmed.²² The greatest bias in PAF occurs when sensitivity is poor in a measure for a common risk factor (e.g., smoking).²⁸ We have demonstrated the extent of such bias, but a formal correction with adjustment for confounding requires innovative methodology, to be further pursued.^{24,29} The observed effect of substance use may be accounted for in part by unmeasured adverse socio-economic condition and/or inadequate access to pre-natal care. A differential error may have biased the results if mother's health during pregnancy was related to substance use and also influenced her recall. Finally, some high-risk and at-home deliveries will not have been captured and this may have resulted in under-representation of remote and marginalized communities.

It is reasonable to ask the relevance of early neonatal morbidity to long-term health outcomes. Low Apgar is not currently considered to be a good predictor of long-term ill health⁸ despite recent suggestions that it may be related to risk of death and cerebral palsy,⁹ minor disabilities at school age,¹⁰ as well as neurological disability and cognitive function deficit in adults.³⁰ We do not know whether NICU admission and resuscitation are, of themselves, correlates of long-term ill health but we do know that avoidance of these costly specialist procedures would free resources for use elsewhere in the health care system. We conclude that in preventing early neonatal morbidity among singleton births in Alberta, control of maternal smoking would be a fruitful and efficient strategy, while acknowledging that established interventions in this group have only modest success.³¹

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RÉSUMÉ

Contexte : Il y a peu d'études (et il n'y en a eu aucune au Canada) sur le lien entre le tabagisme maternel, la consommation d'alcool et la toxicomanie durant la grossesse et la morbidité néonatale précoce.

Méthode : Nous avons analysé les dossiers des naissances vivantes uniques en Alberta, au Canada. Les marqueurs de la morbidité néonatale étaient le score d'Apgar (<7 à 5 minutes post-partum) et les mesures de réanimation (2001-2005, N=191 686), ainsi que les admissions dans les unités de soins néonataux intensifs (2002-2005, N=154 924). Par analyse de régression logistique, nous avons estimé les rapports de cotes (RC) pour la consommation autodéclarée d'alcool ou de drogue et la santé maternelle avant la conception, en rajustant les données selon l'âge de la mère, la parité, l'année et le sexe du fœtus. Les RC univariés et les fractions étiologiques du risque ont été calculés avec et sans rajustements pour la sous-notification de la consommation d'alcool et de drogue.

Résultats : Le facteur de risque le plus courant était le tabagisme maternel durant la grossesse; il concernait 20 % des mères selon leurs propres déclarations, et ce chiffre pourrait être deux fois plus élevé si l'on tient compte de la sous-notification. Le tabagisme (RC 1,2), la consommation d'alcool (RC 1,2-1,5) et la toxicomanie (RC 1,7-2) de la mère durant la grossesse étaient associés à des risques accrus pour chacun des marqueurs de la morbidité néonatale précoce ($p < 0,05$, compte tenu des covariables). En éliminant le plus courant de ces facteurs de risque (le tabagisme maternel), on préviendrait entre 10 et 15 % des trois marqueurs de morbidité néonatale. Les autres facteurs en dossier liés à la santé de la mère avant la conception, malgré certaines associations importantes, n'étaient responsables que d'une petite proportion des cas.

Discussion : Nous en concluons que pour prévenir la morbidité néonatale précoce parmi les naissances uniques en Alberta, le contrôle du tabagisme maternel (le plus courant des facteurs de risque potentiellement modifiables) demeure un objectif important.

Mots clés : grossesse; épidémiologie; néonatalogie; troubles liés à une substance; tabagisme