


ORIGINAL ARTICLE

Pregnancy outcomes in women with anorexia nervosa

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Abstract

Objective: Birth outcomes of women with anorexia nervosa are poorly understood. We hypothesized that hospitalization for anorexia nervosa before or during pregnancy is associated with an elevated risk of adverse maternal and infant birth outcomes.

Method: We performed a retrospective cohort study of 2,134,945 pregnancies in Quebec, Canada, from 1989 to 2016. The main exposure measure was anorexia nervosa requiring hospital treatment before or during pregnancy. Outcome measures included stillbirth, preterm birth, low birth weight, small-for-gestational age birth, pre-eclampsia, gestational diabetes, cesarean delivery, and other pregnancy disorders. We computed risk ratios and 95% confidence intervals (CI) for the association between anorexia nervosa and birth outcomes adjusted for maternal characteristics.

Results: Compared with no hospitalization, anorexia nervosa hospitalization was associated with 1.99 times the risk of stillbirth (95% CI 1.20–3.30), 1.32 times the risk of preterm birth (95% CI 1.13–1.55), 1.69 times the risk of low birth weight (95% CI 1.44–1.99), and 1.52 times the risk of small-for-gestational age birth (95% CI 1.35–1.72). The associations with low birth weight and small-for-gestational age birth were more prominent in women hospitalized for anorexia nervosa during pregnancy or within 2 years of delivery. Hospitalization for anorexia nervosa was associated with certain maternal outcomes, including precipitate labor, acute liver failure, and admission to an intensive care unit.

Discussion: Hospitalization for anorexia nervosa before or during pregnancy is associated with adverse infant and maternal outcomes. Infants are primarily at risk of stillbirth, preterm birth, low birth weight, and small-for-gestational age birth.

KEYWORDS

anorexia nervosa, eating disorder, obstetric complications, pregnancy, retrospective study

1 | INTRODUCTION

Anorexia nervosa is a severe psychiatric disorder that affects 1% of women of childbearing age (Smink, van Hoeken, & Hoek, 2012), but pregnancy outcomes of these women are poorly understood. Women with anorexia nervosa have severely restricted diets and may be malnourished (Setnick, 2010), potentially increasing the risk of

complications at birth. Prior studies have found that malnutrition is associated with preterm birth, low birth weight, and restricted fetal growth (Abu-Saad & Fraser, 2010). In some data, extreme malnutrition due to famine during pregnancy is associated with an elevated risk of neonatal mortality (Hernández-Julián, Mansour, & Peters, 2014). Others have shown that fasting, even if not accompanied by malnutrition, increases the risk of preterm birth, gestational diabetes, and

cesarean delivery (Mirghani & Hamud, 2006; Tith, Bilodeau-Bertrand, Lee, Healy-Profitts, & Auger, 2019). In addition, severe anorexia nervosa can lead to cardiac arrhythmias and structural abnormalities, electrolyte imbalance, pancytopenias, and liver steatosis, which may further complicate pregnancies (Westmoreland, Krantz, & Mehler, 2016).

Existing data on the relationship between anorexia nervosa and birth outcomes are conflicting. Some studies report that anorexia nervosa increases the risk of cesarean delivery, miscarriage, preterm birth, and small-for-gestational age birth (Bulik et al., 1999; Eik-Nes et al., 2018; Linna et al., 2014), whereas others find no association (Bulik et al., 2009; Ekéus, Lindberg, Lindblad, & Hjern, 2006; Micali et al., 2012). Most analyses are, however, limited to small numbers of women with anorexia nervosa (Bulik et al., 1999; Bulik et al., 2009; Eagles, Lee, Raja, Millar, & Bhattacharya, 2012; Micali et al., 2012), or do not assess whether anorexia nervosa is severe or active during pregnancy (Eik-Nes et al., 2018; Linna et al., 2014). In a study of 1,609 women in Denmark, both active and past anorexia nervosa were associated with low birth weight and small-for-gestational age birth (Micali, Stemmann Larsen, Strandberg-Larsen, & Nybo Andersen, 2016), but the association with other obstetric outcomes was not investigated. Thus, the overall picture of how anorexia nervosa may influence maternal and fetal outcomes is unclear. Owing to the findings of previous studies, we hypothesized that anorexia nervosa would be associated with a range of pregnancy outcomes in mothers and infants. In this study, we evaluated the association of anorexia nervosa that required hospitalization with adverse birth outcomes in a large cohort of pregnancies containing information on the status and severity of anorexia nervosa.

2 | MATERIALS AND METHODS

2.1 | Study design and population

We performed a retrospective cohort study of 2,134,945 singleton pregnancies in Quebec, Canada from 1989 to 2016. We extracted data on pregnancies from the Maintenance and Use of Data for the Study of Hospital Clientele registry, an administrative dataset that contains discharge summaries of all inpatient hospitalizations in Quebec (Ayoub et al., 2018). These data include 99% of deliveries in the province, and are therefore representative of the population. We included singleton births at ≥ 20 weeks of gestation in the analysis. The cohort was restricted to women with valid medical insurance numbers because this information was needed to follow women over time. Requests to access the dataset should be sent to the Ministry of Health and Social Services following standard protocols.

2.2 | Anorexia nervosa

The primary exposure measure was hospitalization for anorexia nervosa before or during pregnancy (yes/no). We determined the total number of anorexia nervosa hospitalizations (0, 1, ≥ 2) and the interval between

the most recent hospitalization and delivery (< 2 , 2–4, ≥ 5 years) to assess the potential impact of severity and disease activity on birth outcomes. We used the 9th and 10th revisions of the International Classifications of Diseases (ICD) to identify women with anorexia nervosa. The definition of anorexia nervosa in the ICD follows diagnostic criteria in the Diagnostic and Statistical Manual of Mental disorders, which considers significant weight loss, fear of weight gain, and disturbed body image as essential clinical features (Ekéus et al., 2006; Linna et al., 2014). In Canada, hospitalization is required for hemodynamic instability, electrolytic imbalance, acute medical complications including hematemesis and syncope, as well as rapid or constant weight loss, acute refusal to eat, excessive purgatory behaviors, and inability to function at school, work, or socially (Golden et al., 2015).

We stratified women according to whether the most recent anorexia nervosa hospitalization was before or during pregnancy. We also classified women with anorexia nervosa based on presence of bulimia nervosa after 2006, the year these data became available. Anorexia nervosa is sometimes followed by bulimia nervosa, and evidence suggests that birth outcomes may differ for women with both eating disorders (Micali et al., 2016). Women with no admission for anorexia nervosa any time during the study comprised the reference group in all comparisons.

2.3 | Birth outcomes

We examined several outcomes at delivery (Table S1). Maternal outcomes included preeclampsia, placental abruption, placenta previa, antepartum hemorrhage, postpartum hemorrhage, oligohydramnios, polyhydramnios, gestational diabetes, sepsis and other infections, cardiovascular disorders, renal disorders, acute liver failure, severe maternal morbidity, blood transfusion, and intensive care unit admission. Severe maternal morbidity was a composite variable which included life-threatening conditions such as shock and eclampsia (Dzakpasu et al., 2019). We also identified complications of labor and delivery, including cesarean delivery, breech presentation, instrumental delivery (forceps, vacuum), perineal laceration, premature rupture of membranes, precipitate labor, and other complications (failed induction of labor, abnormal forces of labor, obstructed labor, prolonged labor, retained placenta, umbilical cord complications).

Infant outcomes included stillbirth, death before discharge, preterm birth at < 37 weeks of gestation, low birth weight $< 2,500$ g, small-for-gestational age birth, and large-for-gestational age birth. We defined small-for-gestational age and large-for-gestational age birth as infants with weight below the 10th percentile and above the 90th percentile, respectively, for gestational age and sex (Kramer et al., 2001). Secondary infant outcomes included neonatal sepsis, jaundice, birth trauma, respiratory disorders (asphyxia, congenital pneumonia, aspiration, interstitial emphysema, pulmonary hemorrhage, atelectasis, and others), cardiovascular disorders (cardiac failure, dysrhythmia, hypertension, myocardial ischemia, and others), metabolic disorders (hypoglycemia, calcium and magnesium imbalance, thyroid disorders, electrolyte disturbances, metabolic acidosis, and others), severe morbidity (necrotizing enterocolitis, intracranial hemorrhage, bronchopulmonary dysplasia, retinopathy of

prematurity, patent ductus arteriosus, respiratory distress syndrome), blood transfusion, intubation, and neonatal intensive care unit admission. We included three congenital anomalies (heart, urinary, clubfoot defects) that were frequent in women with anorexia nervosa in our data.

2.4 | Covariates

We accounted for potential confounders of the association between anorexia nervosa and birth outcomes based on previous literature

(Zipfel, Giel, Bulik, Hay, & Schmidt, 2015). Covariates included maternal age at delivery (<20, 20–24, 25–29, 30–34, ≥35 years), parity (0, 1, ≥2), comorbid mental disorders (bipolar disorder, depression, schizophrenia, anxiety and stress-related disorders), preexisting metabolic disorders (obesity, type 1 or 2 diabetes, hypertension), substance use (tobacco, alcohol, illicit drugs) (Table S1), socioeconomic status (advantaged, moderately advantaged, middle, moderately disadvantaged, disadvantaged, unknown), place of residence (rural, urban, unknown), and time period at delivery (1989–1997, 1998–2006, 2007–2016). Socioeconomic status was captured using a composite

TABLE 1 Distribution of maternal characteristics

	No. births (%)		p-value
	Anorexia	No anorexia	
Maternal age, years			<.0001
<20	77 (4.0)	76,532 (3.6)	
20–24	400 (20.9)	371,825 (17.4)	
25–29	701 (36.7)	754,878 (35.4)	
30–34	567 (29.7)	640,923 (30.0)	
≥35	165 (8.6)	288,876 (13.5)	
Parity			<.0001
0	1,016 (53.2)	1,203,271 (56.4)	
1	597 (31.3)	680,677 (31.9)	
≥2	297 (15.5)	249,087 (11.7)	
Comorbid mental disorders ^a			<.0001
Yes	100 (5.2)	11,236 (0.5)	
No	1,810 (94.8)	2,121,799 (99.5)	
Preexisting metabolic disorders ^b			.1741
Yes	41 (2.2)	56,437 (2.6)	
No	1,869 (97.9)	2,076,598 (97.4)	
Substance use ^c			<.0001
Yes	51 (2.7)	32,624 (1.5)	
No	1,859 (97.3)	2,100,411 (98.5)	
Socioeconomic status			<.0001
Advantaged	357 (18.7)	376,955 (17.7)	
Moderately advantaged	392 (20.5)	403,830 (18.9)	
Middle	403 (21.1)	404,965 (19.0)	
Moderately disadvantaged	374 (19.6)	405,556 (19.0)	
Disadvantaged	299 (15.7)	420,001 (19.7)	
Place of residence			.2420
Rural	352 (18.4)	409,420 (19.2)	
Urban	1,529 (80.1)	1,659,539 (77.8)	
Time period			<.0001
1989–1997	127 (6.6)	770,268 (36.1)	
1998–2006	547 (28.6)	630,819 (29.6)	
2007–2016	1,236 (64.7)	731,948 (34.3)	
Total	1,910 (100.0)	2,133,035 (100.0)	

^aBipolar disorder, depression, schizophrenia, anxiety and stress-related disorders.

^bObesity, type 1 or 2 diabetes, hypertension.

^cTobacco, alcohol, illicit drugs.

of neighborhood-based mean income, educational level, and employment rate from census data in Quebec (Pampalon & Raymond, 2000). Covariates were measured at delivery.

2.5 | Data analysis

In primary analyses, we calculated rates of adverse birth outcomes per 1,000 births. To determine the association between anorexia nervosa and birth outcomes, we estimated risk ratios (RR) and 95% confidence intervals (CI) using log-binomial regression. We adjusted for potential confounders, including maternal age, parity, comorbid mental disorders, preexisting metabolic disorders, substance use, socioeconomic status, place of residence, and time period at delivery. We employed generalized estimating equations to account for correlation due to repeated births in the same woman.

In secondary analyses, we selected the three most frequent adverse birth outcomes associated with anorexia nervosa, and assessed the relationship with the (a) total number of anorexia nervosa hospitalizations, (b) time between the most recent

hospitalization and delivery, (c) whether the first hospitalization was before or during pregnancy, and (d) presence of bulimia nervosa.

In sensitivity analyses, we examined women with other mental health comorbidities, and recurrence of outcomes in women with more than one pregnancy. We accounted for multiple comparisons using the Holm method for 95% CIs (Ludbrook, 2000). We performed the analysis in SAS v9.4 (SAS Institute Inc., Cary, NC). This study complied with Tri-Council Policy requirements for research in Canada. Data were de-identified and informed consent was not required. The institutional review board of the University of Montreal Hospital Centre waived ethics review.

2.6 | Results

In this cohort of 2,134,945 pregnancies, 1,910 births (0.1%) were in women with anorexia nervosa before or during pregnancy (Table 1). Women admitted for anorexia nervosa had more comorbid mental disorders (5.2%) than other women (0.5%). Similarly, women admitted for anorexia nervosa had more substance use disorders (2.7%) than

TABLE 2 Association between anorexia nervosa and adverse maternal outcomes

	Anorexia		No anorexia		Risk ratio (95% confidence interval)	
	No. outcomes	Rate per 1,000	No. outcomes	Rate per 1,000	Unadjusted	Adjusted ^a
Preeclampsia	49	25.7	61,342	28.8	0.89 (0.68–1.18)	0.77 (0.58–1.02)
Placental abruption	53	27.7	41,679	19.5	1.42 (1.09–1.85)	1.29 (0.99–1.69)
Placenta previa	10	5.2	10,998	5.2	1.02 (0.55–1.88)	0.96 (0.52–1.78)
Antepartum hemorrhage	61	31.9	53,757	25.2	1.27 (0.99–1.62)	1.22 (0.95–1.57)
Postpartum hemorrhage	90	47.1	113,731	53.3	0.88 (0.72–1.08)	0.76 (0.62–0.93)
Oligohydramnios	27	14.1	31,081	14.6	0.97 (0.67–1.41)	0.82 (0.56–1.20)
Polyhydramnios	21	11.0	19,857	9.3	1.18 (0.77–1.81)	0.95 (0.62–1.46)
Gestational diabetes	63	33.0	108,262	50.8	0.65 (0.51–0.83)	0.57 (0.44–0.73)
Sepsis and other infections	78	40.8	97,725	45.8	0.89 (0.72–1.11)	0.82 (0.66–1.03)
Cardiovascular disorder	8	4.2	4,928	2.3	2.10 (0.68–6.51)	1.52 (0.76–3.04)
Renal disorder	<5	<1.7	1,595	0.7	1.81 (0.91–3.62)	1.82 (0.58–5.65)
Acute liver failure	14	7.3	5,484	2.6	2.85 (1.69–4.81)	1.90 (1.12–3.21)
Severe maternal morbidity ^b	49	25.7	50,049	23.5	1.09 (0.83–1.44)	1.07 (0.81–1.43)
Blood transfusion	12	6.3	14,277	6.7	0.94 (0.53–1.65)	0.82 (0.47–1.45)
Intensive care unit	12	6.3	5,799	2.7	2.31 (1.31–4.06)	1.86 (1.06–3.28)
Cesarean delivery	357	186.9	422,579	198.1	0.94 (0.86–1.04)	0.91 (0.82–1.01)
Breech presentation	87	45.5	83,716	39.2	1.16 (0.95–1.43)	1.15 (0.93–1.42)
Instrumental delivery	195	102.1	263,114	123.4	0.83 (0.72–0.95)	0.87 (0.77–1.02)
Perineal laceration	938	491.1	950,467	445.6	1.10 (1.05–1.15)	0.97 (0.91–1.04)
Premature rupture of membrane	190	99.5	164,125	76.9	1.29 (1.13–1.50)	1.07 (0.93–1.24)
Precipitate labor	64	33.5	35,218	16.5	2.03 (1.59–2.58)	1.43 (1.12–1.82)
Other complications of labor ^c	560	293.2	718,255	336.7	0.87 (0.81–0.93)	0.87 (0.80–0.94)

^aRisk ratio for anorexia versus no anorexia, adjusted for maternal age, parity, comorbid mental disorders, preexisting metabolic disorders, substance use, socioeconomic status, place of residence, and time period at delivery.

^bSurgical complications, embolism, shock, uterine rupture, severe hemorrhage, and other serious adverse obstetric outcomes (Dzakpasu et al., 2019).

^cFailed induction of labor, abnormal forces of labor, obstructed labor, prolonged labor, retained placenta, umbilical cord complications.

other women (1.5%). Characteristics such as maternal age, parity, socioeconomic status, place of residence, and time period at delivery were comparable between women with and without anorexia nervosa.

Hospitalization for anorexia nervosa before or during pregnancy was not associated with most adverse maternal outcomes (Table 2). In adjusted models, anorexia nervosa was not associated with pre-eclampsia, placenta previa, cesarean delivery, sepsis and other infections, blood transfusion, severe morbidity, and most complications of labor and delivery. However, women with anorexia nervosa admissions had 1.43 times the risk of precipitate labor (95% CI 1.12–1.82), 1.90 times the risk of acute liver failure (95% CI 1.12–3.21), and 1.86 times the risk of intensive care unit admission (95% CI 1.06–3.28), compared with no anorexia nervosa. Women with anorexia nervosa had a lower risk of postpartum hemorrhage (RR 0.76, 95% CI 0.62–0.93) and gestational diabetes (RR 0.57, 95% CI 0.44–0.73).

Women with anorexia nervosa admissions had a greater risk of several adverse infant outcomes compared with no anorexia nervosa (Table 3). In adjusted models, hospitalization for anorexia nervosa was associated with 1.99 times the risk of stillbirth (95% CI 1.20–3.30),

1.32 times the risk of preterm birth (95% CI 1.13–1.55), 1.69 times the risk of low birth weight (95% CI 1.44–1.99), 1.52 times the risk of small-for-gestational age birth (95% CI 1.35–1.72), and 1.33 times the risk of neonatal intensive care unit admission (95% CI 1.09–1.62), compared with no anorexia nervosa. Anorexia nervosa was associated with neonatal jaundice (RR 1.11, 95% CI 1.00–1.24), cardiovascular disorders (RR 1.27, 95% CI 1.03–1.56), and respiratory disorders (RR 1.16, 95% CI 1.02–1.31). However, women hospitalized for anorexia nervosa were less likely to have large-for-gestational age infants (RR 0.66, 95% CI 0.54–0.80).

Women with more recent hospitalizations for anorexia nervosa were at greatest risk of adverse infant outcomes (Table 4). Relative to no admissions, anorexia nervosa admissions within 2 years of delivery were associated with 1.92 times the risk of preterm birth (95% CI 1.32–2.80), whereas admissions within 2–4 years of delivery were associated with 1.37 times the risk (95% CI 0.92–2.02) and admissions ≥ 5 years prior were associated with 1.21 times the risk (95% CI 0.98–1.47). Findings were generally similar for low birth weight and small-for-gestational age birth. Anorexia nervosa was associated with all three outcomes regardless of the total number of admissions.

TABLE 3 Association between anorexia nervosa and adverse infant outcomes

	Anorexia		No anorexia		Risk ratio (95% confidence interval)	
	No. outcomes	Rate per 1,000	No. outcomes	Rate per 1,000	Unadjusted	Adjusted ^a
Stillbirth	15	7.9	8,476	4.0	1.98 (1.19–3.27)	1.99 (1.20–3.30)
Death before discharge	5	2.6	4,883	2.3	1.15 (0.48–2.76)	1.16 (0.48–2.78)
Preterm birth <37 weeks	154	81.3	128,814	60.6	1.34 (1.15–1.56)	1.32 (1.13–1.55)
Low birth weight < 2,500 g ^b	144	76.0	95,887	45.1	1.68 (1.44–1.97)	1.69 (1.44–1.99)
Small-for-gestational age birth ^c	269	142.0	219,476	103.3	1.37 (1.23–1.54)	1.52 (1.35–1.72)
Large-for-gestational age birth ^c	104	54.9	176,841	83.2	0.66 (0.55–0.79)	0.66 (0.54–0.80)
Neonatal sepsis	33	17.4	23,873	11.2	1.55 (1.10–2.17)	1.07 (0.76–1.50)
Neonatal jaundice	330	174.1	348,106	163.8	1.06 (0.96–1.17)	1.11 (1.00–1.24)
Birth trauma	91	48.0	94,986	44.7	1.07 (0.88–1.31)	0.99 (0.81–1.22)
Respiratory disorder	247	130.3	245,635	115.6	1.12 (1.00–1.27)	1.16 (1.02–1.31)
Cardiovascular disorder	90	47.5	42,521	20.0	2.37 (1.94–2.90)	1.27 (1.03–1.56)
Metabolic disorders	101	53.3	98,311	46.3	1.15 (0.95–1.39)	1.02 (0.84–1.23)
Severe morbidity ^d	16	8.4	19,389	9.1	0.93 (0.57–1.51)	1.16 (0.71–1.89)
Blood transfusion	10	5.3	6,723	3.2	1.67 (0.90–3.10)	1.41 (0.76–2.63)
Intubation	21	11.1	14,099	6.6	1.67 (1.09–2.56)	1.26 (0.82–1.94)
Intensive care unit	100	52.8	60,837	28.6	1.84 (1.52–2.23)	1.33 (1.09–1.62)
Congenital anomaly						
Heart	18	9.5	18,104	8.5	1.11 (0.70–1.77)	1.06 (0.67–1.69)
Urinary	20	10.6	15,153	7.1	1.48 (0.96–2.29)	1.19 (0.77–1.84)
Clubfoot	31	16.4	29,319	13.8	1.19 (0.84–1.68)	1.34 (0.94–1.91)

^aRisk ratio for anorexia versus no anorexia, adjusted for maternal age, parity, comorbid mental disorders, preexisting metabolic disorders, substance use, socioeconomic status, place of residence, and time period at delivery.

^bExcludes 35 deliveries missing birth weight.

^cExcludes 1,243 deliveries missing data on small-for-gestational age birth and large-for-gestational age birth.

^dNecrotizing enterocolitis, intracranial hemorrhage, bronchopulmonary dysplasia, retinopathy of prematurity, patent ductus arteriosus, respiratory distress syndrome.

TABLE 4 Severity of anorexia nervosa and risk of growth-related infant outcomes

				Risk ratio (95% confidence interval)	
	Total births	No. outcomes	Rate per 1,000	Unadjusted	Adjusted ^a
Preterm birth					
No. admissions for anorexia					
2 or more	668	52	77.8	1.28 (0.99–1.67)	1.27 (0.97–1.67)
1	1,227	102	83.1	1.37 (1.14–1.65)	1.35 (1.11–1.64)
No anorexia	2,124,559	128,814	60.6	Reference	Reference
Most recent admission					
<2 years before delivery	205	27	131.7	2.17 (1.53–3.09)	1.92 (1.32–2.80)
2–4 years before delivery	266	25	94.0	1.55 (1.07–2.25)	1.37 (0.92–2.02)
≥5 years before delivery	1,424	102	71.6	1.18 (0.98–1.42)	1.21 (0.98–1.47)
No anorexia	2,124,559	128,814	60.6	Reference	Reference
Low birth weight < 2,500 g ^b					
No. admissions for anorexia					
2 or more	668	52	77.8	1.72 (1.33–2.24)	1.74 (1.33–2.29)
1	1,227	92	75.0	1.66 (1.36–2.02)	1.66 (1.35–2.04)
No anorexia	2,124,559	95,887	45.1	Reference	Reference
Most recent admission					
<2 years before delivery	205	28	136.6	3.03 (2.14–4.27)	2.62 (1.81–3.79)
2–4 years before delivery	266	18	67.7	1.50 (0.96–2.34)	1.32 (0.83–2.09)
≥5 years before delivery	1,424	98	68.8	1.52 (1.26–1.85)	1.61 (1.32–1.96)
No anorexia	2,124,559	95,887	45.1	Reference	Reference
Small-for-gestational age birth ^c					
No. admissions for anorexia					
2 or more	668	97	145.2	1.40 (1.17–1.69)	1.57 (1.29–1.91)
1	1,227	172	140.2	1.36 (1.18–1.56)	1.50 (1.29–1.74)
No anorexia	2,124,559	219,476	103.3	Reference	Reference
Most recent admission					
<2 years before delivery	205	41	200.0	1.93 (1.47–2.54)	1.83 (1.35–2.49)
2–4 years before delivery	266	45	169.2	1.64 (1.25–2.14)	1.52 (1.14–2.04)
≥5 years before delivery	1,424	183	128.5	1.24 (1.09–1.42)	1.47 (1.27–1.70)
No anorexia	2,124,559	219,476	103.3	Reference	Reference

^aRisk ratio for anorexia versus no anorexia, adjusted for maternal age, parity, comorbid mental disorders, preexisting metabolic disorders, substance use, socioeconomic status, place of residence, and time period at delivery.

^bExcludes 35 deliveries missing birth weight.

^cExcludes 1,243 deliveries missing data on small-for-gestational age birth.

The association between anorexia nervosa and adverse infant outcomes was present whether hospitalization occurred before or during pregnancy (Table 5). However, hospitalization during pregnancy was more strongly associated with adverse outcomes. Relative to no admission, anorexia nervosa admission during pregnancy was associated with 3.0 times the risk of small-for-gestational age birth (95% CI 1.87–4.83), whereas admission before pregnancy was associated with 1.47 times the risk (95% CI 1.30–1.67). A similar pattern was present for low birth weight. For preterm birth, only admission before pregnancy was associated with a greater risk (RR 1.35, 95% CI 1.15–1.58). Women with both anorexia and bulimia nervosa had 2.01

times the risk of preterm birth (95% CI 1.11–3.64) compared with no hospitalization for these disorders, whereas women with only anorexia nervosa had 1.32 times the risk (95% CI 1.12–1.55). A similar trend was present for low birth weight.

In sensitivity analyses, women with anorexia nervosa and other mental health comorbidities had 2.02 times the risk of low birth weight (95% CI 1.09–3.75) compared with no hospitalization for these disorders, whereas women with isolated anorexia nervosa had 1.70 times the risk (95% CI 1.44–2.02; Table S2). Among 630 women with anorexia nervosa who had more than one pregnancy, preterm birth recurred in 11.9%, low birth weight in 18.5%, and small-for-

TABLE 5 Timing of anorexia nervosa hospitalization and presence of bulimia nervosa in relation to growth-related infant outcomes

				Risk ratio (95% confidence interval)	
	Total births	No. outcomes	Rate per 1,000	Unadjusted	Adjusted ^a
Preterm birth					
Time of admission					
Anorexia before pregnancy	1,842	152	82.5	1.36 (1.17–1.59)	1.35 (1.15–1.58)
Anorexia during pregnancy	53	<5	37.7	0.62 (0.16–2.42)	0.53 (0.13–2.13)
No anorexia	2,124,559	128,814	60.6	Reference	Reference
Comorbid eating disorder					
Anorexia and bulimia	86	11	127.9	2.11 (1.21, 3.66)	2.01 (1.11, 3.64)
Anorexia without bulimia	1,809	143	79.0	1.30 (1.11, 1.53)	1.32 (1.12, 1.55)
No anorexia	2,124,559	128,814	60.6	Reference	Reference
Low birth weight ^b					
Time of admission					
Before pregnancy	1,842	137	74.4	1.65 (1.40–1.94)	1.67 (1.41–1.97)
During pregnancy	53	7	132.1	2.93 (1.47–5.84)	2.40 (1.14–5.02)
No anorexia	2,124,559	95,887	45.1	Reference	Reference
Comorbid eating disorder					
Anorexia and bulimia	86	11	127.9	2.83 (1.63, 4.92)	2.63 (1.45, 4.74)
Anorexia without bulimia	1,809	133	73.5	1.63 (1.38, 1.92)	1.67 (1.41, 1.98)
No anorexia	2,124,559	95,887	45.1	Reference	Reference
Small-for-gestational age birth ^c					
Time of admission					
Before pregnancy	1,842	252	136.8	1.32 (1.18–1.49)	1.47 (1.30–1.67)
During pregnancy	53	17	320.8	3.10 (2.10–4.59)	3.00 (1.87–4.83)
No anorexia	2,124,559	219,476	103.3	Reference	Reference
Comorbid eating disorder					
Anorexia and bulimia	86	13	151.2	1.46 (0.89, 2.41)	1.61 (0.93, 2.77)
Anorexia without bulimia	1,809	256	141.5	1.37 (1.22, 1.53)	1.52 (1.35, 1.72)
No anorexia	2,124,559	219,476	103.3	Reference	Reference

^aRisk ratio for anorexia versus no anorexia, adjusted for maternal age, parity, comorbid mental disorders, preexisting metabolic disorders, substance use, socioeconomic status, place of residence, and time period at delivery.

^bExcludes 35 deliveries missing birth weight.

^cExcludes 1,243 deliveries missing data on small-for-gestational age birth.

gestational age birth in 20.6% of women. In women without anorexia nervosa, there was no consistent difference in recurrence of preterm birth (16.3%), low birth weight (14.6%), and small-for-gestational age birth (21.1%). Accounting for multiple comparisons did not change the interpretation of results for preterm birth, low birth weight, or small-for-gestational age birth (Tables S3 and S4).

3 | DISCUSSION

In this retrospective cohort study of more than 2 million singleton pregnancies, women admitted for anorexia nervosa had a greater risk of adverse infant outcomes, including stillbirth, preterm birth, low birth weight, small-for-gestational age birth, certain neonatal disorders, and admission to neonatal intensive care units. Anorexia nervosa

hospitalization was associated with precipitate labor, acute liver failure, and admission to intensive care unit, but not other adverse maternal outcomes. The association of anorexia nervosa with infant outcomes was strongest for women who were hospitalized during pregnancy or within 2 years of delivery. These findings suggest that women hospitalized for anorexia nervosa have a greater risk of poor fetal growth, particularly when hospitalization is closer to pregnancy.

Very little is known on the relationship between anorexia nervosa and maternal outcomes at delivery. Existing evidence is limited to small samples of women with data from self-report (Bulik et al., 2009; Micali et al., 2012) and inpatient/outpatient clinics (Bulik et al., 1999; Eagles et al., 2012), or to selected pregnancy complications among inpatients (Ekéus et al., 2006; Linna et al., 2014). A Swedish study of 1,000 women with prior hospitalizations for anorexia nervosa reported no association with adverse maternal outcomes, but focused

primarily on preeclampsia, premature rupture of membranes, cesarean delivery, and instrumental delivery (Ekéus et al., 2006). A study of 66 women with inpatient and outpatient data on anorexia nervosa in New Zealand found no association with preeclampsia, postpartum hemorrhage and infection, induced labor, breech presentation, forceps delivery, and retained placenta (Bulik et al., 1999). Our study in a large cohort of women suggests that anorexia nervosa is not associated with most maternal complications. As anorexia nervosa reduces the risk of obesity, outcomes such as preeclampsia, gestational diabetes, and cesarean delivery may be less common (Vinturache, Moledina, McDonald, Slater, & Tough, 2014).

Nevertheless, our findings suggest that women with anorexia nervosa had an increased risk of precipitate labor, acute liver failure, and admission to intensive care unit. Although the number of women with these outcomes was low, multiple factors could contribute to these associations. Precipitate labor is more common during preterm delivery due to the smaller size of infants (Suzuki, 2015). In our data, women with anorexia nervosa had an increased risk of preterm delivery. Illicit substances such as cocaine, a risk factor for rapid uterine contractions, may also contribute to the risk of precipitate labor (Cook et al., 2017). Although we adjusted for substance use, it is possible that this variable is underreported. Acute liver failure may be related to liver damage from the prolonged starvation associated with severe anorexia nervosa (Kheloufi, Boulanger, Durand, & Rautou, 2014). Factors contributing to the risk of admission to intensive care unit are unclear, but may relate to acute liver failure. Organ failure is common in obstetric patients requiring intensive care (Vasquez et al., 2007).

A larger body of literature has focused on the association of anorexia nervosa with neonatal outcomes. A study of 182 women hospitalized for anorexia nervosa in Finland found associations with perinatal death, very preterm birth, low birth weight, and small-for-gestational age birth (Linna et al., 2014), similar to our own results. The association of anorexia nervosa with low birth weight and small-for-gestational age birth has also been observed elsewhere (Eagles et al., 2012; Eik-Nes et al., 2018; Micali et al., 2016). However, not all studies have found an increased risk of these outcomes (Bulik et al., 2009; Ekéus et al., 2006; Micali et al., 2012), although it is possible that differences in study design account for these discrepancies. Except for one analysis of inpatient data (Ekéus et al., 2006), negative studies mostly used self-reported data (Bulik et al., 2009; Micali et al., 2012). In studies suggesting a harmful impact of anorexia nervosa, investigators used inpatient data similar to ours (Eik-Nes et al., 2018) or a combination of inpatient and outpatient data (Eagles et al., 2012). We found that anorexia nervosa was associated with infant outcomes not included in previous studies, including jaundice, cardiovascular disorders, respiratory disorders, and admission to neonatal intensive care units. These results provide added support for an association between anorexia nervosa and adverse infant outcomes known to be related to preterm birth (Saigal & Doyle, 2008).

Our findings suggest that more recent hospitalizations for anorexia nervosa are associated with a particularly elevated risk of several adverse infant outcomes. Risks of preterm birth, low birth weight, and small-for-gestational age birth were all greater for women

hospitalized with anorexia nervosa during pregnancy or within 2 years of delivery. Risks were not as elevated when the most recent hospitalization was more than 2 years before delivery, suggesting either recovery or less active disease. However, risks persisted somewhat even when the last hospitalization was over 5 years before delivery, indicating that a substantial number of women may have treatment-resistant anorexia nervosa.

The bulk of our results suggests that most of the relationship between anorexia nervosa and birth complications relates to poor fetal growth. Low calorie and protein intake leads to low body mass index, a risk factor for preterm birth, low birth weight, and small-for-gestational age birth (Liu et al., 2016). Studies suggest that low pre-pregnancy body mass is associated with reduced uteroplacental blood flow which may compromise transfer of nutrients to the fetus (Mayer & Joseph, 2013). This problem may be exacerbated by the poor nutritional content of diets in women with anorexia nervosa (Setnick, 2010), as well as by stress and anxiety (Zipfel et al., 2015). Anorexia nervosa is associated with iron, folate, zinc, and vitamin A deficiency (Setnick, 2010), as well as with increased stress and anxiety (Zipfel et al., 2015), factors associated with low birth weight, preterm birth, and restricted fetal growth (Abu-Saad & Fraser, 2010; Cardwell, 2013).

This study has limitations. We used administrative hospital data and were limited to the information available in the dataset. We could only identify women with anorexia nervosa severe enough to require hospitalization, not self-reported anorexia nervosa or anorexia nervosa treated on an outpatient basis only. Women with less severe anorexia nervosa were potentially misclassified, which may have attenuated the magnitude of associations. However, a study of adverse birth outcomes in women with self-reported anorexia nervosa found results similar to ours (Micali et al., 2016). We did not have sufficient power to restrict the analysis to women with atypical anorexia nervosa. These data may include coding errors, and we did not have information on ethnicity, marital status, body mass index, or medication use. We could only adjust the results for available confounders; residual confounding may be possible. Although we adjusted for substance use and comorbid mental disorders, these variables may be underreported. We could not assess gestational weight change, or determine if women with anorexia nervosa who had substantially lower body mass index had even greater risks. Low weight at conception and insufficient weight gain during gestation are associated with adverse neonatal outcomes (Goldstein et al., 2017). Such information would be helpful to determine if there is a threshold below which maternal weight is a considerably greater risk for adverse pregnancy outcomes. Owing to the small number of women hospitalized for anorexia nervosa during pregnancy, results should be interpreted with caution. Finally, the results reflect associations between severe anorexia nervosa and pregnancy outcomes in a large multicultural province in Canada with publicly funded healthcare. We do not know if findings would be similar in other study settings.

In this analysis of 2,134,945 pregnancies in Quebec between 1989 and 2016, anorexia nervosa was associated with stillbirth, preterm birth, low birth weight, and small-for-gestational age birth. The

risks of low birth weight and small-for-gestational age birth were greater for women with anorexia nervosa hospitalizations during pregnancy or within 2 years of delivery. Anorexia nervosa was not associated with most maternal outcomes, but risks of precipitate labor, acute liver failure, and admission to intensive care unit were somewhat elevated. Although more research is needed to confirm these findings, obstetricians and primary care physicians should be aware that women with anorexia nervosa before or during pregnancy have an elevated risk of adverse infant outcomes. These women may merit intensive nutritional rehabilitation and closer monitoring to improve gestational weight gain and growth-related outcomes in their newborns. Follow-up in a high-risk pregnancy clinic should be considered. Pregnant women with active anorexia nervosa may benefit from inpatient care with a multidisciplinary approach to treatment, which may include a combination of weight restoration, psychotherapy, behavioral therapy, and family group psychoeducation (Gentile, Manna, Ciceri, & Rodeschini, 2008). As the rate of unplanned pregnancy among women with anorexia is high (Bulik et al., 2009), greater attention must be paid to informing women about the risk of adverse birth outcomes if anorexia nervosa is left untreated.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Z. A., J. H. P., S. H., and N. A. conceived and designed the study. Z. A., S. H., and E. L. analyzed the data, and all authors interpreted the results. Z. A. drafted the manuscript and all authors revised it critically for important intellectual content. All authors gave final approval of the version to be published. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

Requests to access the dataset should be sent to the Ministry of Health and Social Services following standard protocols.

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Additional supporting information may be found online in the Supporting Information section at the end of this article.

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