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Necrotizing Fasciitis: Association with Pregnancy-related Risk Factors Early in Life

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Background: Pregnancy-related risk factors for necrotizing fasciitis are poorly understood. We investigated pregnancy-related characteristics associated with the long-term risk of developing necrotizing fasciitis, a rare life-threatening infectious disease. **Methods**: We analyzed a longitudinal cohort of 1,344,996 parous women in Quebec, Canada between 1989 and 2020. The main exposure measures included complications of pregnancy such as gestational diabetes, preterm delivery, metabolic disorder, and other maternal characteristics. We followed the women over time to identify future hospitalizations for necrotizing fasciitis up to three decades after delivery. We estimated adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the association of pregnancy characteristics with risk of necrotizing fasciitis in time-varying Cox proportional hazards regression models. **Results**: A total of 420 women were hospitalized for necrotizing fasciitis during follow-up, including 83 (19.8%) with diabetes-related necrotizing fasciitis. The incidence of necrotizing fasciitis was elevated for women with gestational diabetes (2.9 per 100,000 person-years), preterm delivery (3.2 per 100,000 person-years), and metabolic disorders (5.4 per 100,000 person-years), compared with no pregnancy complication (1.1 per 100,000 person-years). Compared with no pregnancy complication, gestational diabetes was associated with 1.87 times the risk (95% CI 1.38-2.53), preterm delivery with 2.10 times the risk (95% CI 1.65-2.66), and metabolic disorder with 3.72 times the risk (95% CI 2.92-4.74) of developing necrotizing fasciitis over time. Pregnancy complications were more strongly associated with the risk of necrotizing fasciitis 5 years or more after delivery. **Conclusions**: Complications of pregnancy may be associated with the long-term risk of necrotizing fasciitis in women.

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Abbreviations: CI, Confidence Interval; HR, Hazard Ratio; SD, Standard Deviation.

Keywords: Cesarean section, Gestational diabetes, Necrotizing fasciitis, Pregnancy complications, Premature birth, Risk factors

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INTRODUCTION

Necrotizing fasciitis is a rare but serious soft tissue infection with an incidence between 0.3 to 15 cases per 100,000 population [1]. Patients at greater risk of necrotizing fasciitis are not fully characterized, although known risk factors include trauma, recent surgery, immunosuppression, diabetes, obesity, and kidney disease [2-4]. Pregnant women are more likely to develop necrotizing fasciitis postpartum [5], with the risk appearing greater following cesarean section [6]. Some data suggest that postpartum hemorrhage, preterm birth, and cesarean section are associated with greater odds of sepsis up to 9 months after delivery [7,8]. While pregnancy appears to be an important contributor to severe infections, the possibility that adverse pregnancy outcomes are associated with the long-term risk of necrotizing fasciitis has not been studied.

Adverse pregnancy outcomes are risk factors for less severe postpartum infections [9-11]. Preeclampsia is associated with urinary tract infections the first month postpartum [9], and manual placenta removal and chorioamnionitis are associated with postpartum endometritis [10,11]. While the relationship with rare infectious diseases has not been studied, adverse pregnancy outcomes such as gestational diabetes and preeclampsia are associated with the development of type 2 diabetes, a known risk factor for necrotizing fasciitis [12,13]. The close relationship between pregnancy complications and metabolic disorders later in life suggests that pregnancy outcomes could predict the long-term risk of necrotizing fasciitis. We assessed whether complications such as preterm birth and gestational diabetes were associated with the future risk of necrotizing fasciitis in a population of parous women.

MATERIALS AND METHODS

Study Design and Population

We carried out a longitudinal cohort study of 1,344,996 women who gave birth in Quebec, Canada between 1989 and 2019. We retrieved the cohort from the Maintenance and Use of Data for the Study of Hospital Clientele registry that contains discharge summaries for all hospitalizations in Quebec, including deliveries [14]. Pregnancy complications during prenatal care, delivery, or postpartum are coded following the International Classification of Diseases. Procedures are coded following the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures and the Canadian Classification of Health Interventions.

Using health insurance numbers, we followed the women prospectively from their first delivery until the time of admission for necrotizing fasciitis. The study ended March 30, 2020, providing up to 31 years of follow-up. We did not include patients who had necrotizing fasciitis before their first delivery, died at delivery, or had missing health insurance numbers (Appendix A: Figure S1). These patients were not eligible for analysis.

Pregnancy Characteristics

We considered several pregnancy complications and general medical conditions as exposures. Pregnancy complications included gestational diabetes, preeclampsia, placental disorders (abruption, accreta, previa, infarction, retention), postpartum hemorrhage, cesarean section, chorioamnionitis, and severe maternal morbidity (intensive care unit admission, assisted ventilation, severe preeclampsia, eclampsia, sepsis, uterine rupture, hysterectomy, surgical complications, severe hemorrhage, embolism, shock, disseminated intravascular coagulation, cardiac conditions, acute renal failure or dialysis, cerebrovascular accidents, other) [15]. We also considered multiple birth, preterm birth (<37 weeks gestation), low birth weight (<2500 g), fetal macrosomia (≥4000 g), and neonatal jaundice as exposures.

General medical conditions included metabolic disorders (obesity, pregestational diabetes, preexisting hypertension, dyslipidemia), immune-related disease (rheumatologic disorders, vasculitis, celiac disease, Graves' disease, Guillain-Barré syndrome, autoimmune thyroiditis, myasthenia gravis, Crohn's disease, ulcerative colitis, other), serious infectious diseases that led to hospitalization before pregnancy, and kidney disease (renal failure, glomerular diseases, urolithiasis, other).

We used diagnostic codes to identify women with these conditions in any pregnancy (Appendix A: Table S1). We expressed pregnancy complications as time-varying covariates to ensure that women were unexposed until the first pregnancy in which a complication appeared [16].

Necrotizing Fasciitis

The outcome was any hospitalization for necrotizing fasciitis during follow-up. Health insurance numbers allowed us to identify admissions anywhere in Quebec between 1989 and 2020. We identified hospitalized patients with diagnostic codes for necrotizing fasciitis and matched them to their delivery hospitalization.

As diabetes frequently clusters with necrotizing fasciitis, we used diagnostic codes from the International Classification of Diseases to determine whether women had coinciding diabetes (Appendix A: Table S1). We thus included both diabetes-related and nondiabetic necrotizing fasciitis.

We had full coverage of necrotizing fasciitis in the population. Because necrotizing fasciitis is life-threaten-

Table 1. Incidence of Necrotizing Fasciitis According to Pregnancy Characteristics

Patient characteristic	Total no. women	No. women with necrotizing fasciitis	Total person-years	Rate per 100,000 person-years (95% CI)
Pregnancy complications				
Gestational diabetes	112,735	49	1,699,171	2.9 (2.2-3.8)
Preeclampsia	76,066	33	1,280,946	2.6 (1.8-3.6)
Placental disorder[a]	118,736	49	2,120,082	2.3 (1.7-3.1)
Postpartum hemorrhage	127,913	47	2,007,406	2.3 (1.8-3.1)
Cesarean section	349,030	152	5,795,591	2.6 (2.2-3.1)
Chorioamnionitis	104,458	33	1,656,346	2.0 (1.4-2.8)
Severe maternal morbidity	55,622	38	980,584	3.9 (2.8-5.3)
Intensive care unit admission	6988	8	103,677	7.7 (3.9-15.4)
Assisted ventilation	819	<5	12,353	24.3 (7.8-75.3)
Severe preeclampsia, eclampsia	19,924	10	319,975	3.1 (1.7-5.8)
Sepsis	7282	9	154,529	5.8 (3.0-11.2)
Surgery-related[b]	14,907	10	298,230	3.4 (1.8-6.2)
Other severe complication[c]	15,747	11	243,055	4.5 (2.5-8.2)
Multiple birth	34,028	19	584,501	3.3 (2.1-5.1)
Preterm birth, <37 weeks	146,643	84	2,604,569	3.2 (2.6-4.0)
Low birth weight, <2500 g	122,452	65	2,162,537	3.0 (2.4-3.8)
Macrosomia, ≥4000 g	196,441	62	3,679,437	1.7 (1.3-2.2)
Neonatal jaundice	341,855	137	6,433,482	2.1 (1.8-2.5)
Medical conditions[d]				
Metabolic disorder	87,948	81	1,486,704	5.4 (4.4-6.8)
Obesity	37,568	42	411,876	10.2 (7.5-13.8)
Pregestational diabetes	21,586	38	447,237	8.5 (6.2-11.7)
Preexisting hypertension	34,788	26	728,809	3.6 (2.4-5.2)
Dyslipidemia	2907	5	42,378	11.8 (4.9-28.3)
Immune-related disease	16,564	10	220,005	4.5 (2.4-8.4)
Prior infectious disease hospitalization	88,837	62	1,351,290	4.6 (3.6-5.9)
Kidney disease	21,097	16	305,472	5.2 (3.2-8.5)
No pregnancy complication	386,523	75	6,979,899	1.1 (0.9-1.3)
Total	1,344,996	420	23,674,870	1.8 (1.6-2.0)

[a]Placenta abruption, accreta, previa, infarction, retention. [b]Hysterectomy, severe uterine rupture, or surgical complications. [c]Severe hemorrhage, embolism, shock, disseminated intravascular coagulation, cardiac conditions, acute renal failure or dialysis, cerebrovascular accident, and other severe complications (adult respiratory distress syndrome, sickle cell anemia with crisis, other). [d]Diagnosed during or before pregnancy.

ing, patients with this disorder require hospitalization for surgical debridement, monitoring, or critical care. Previous validation studies have shown that outcomes in the data have high sensitivity and specificity [17].

Covariates

We accounted for potential confounders, including age at first pregnancy (<25, 25-34, ≥35 years), substance use disorders due to tobacco, alcohol, or drugs (yes, no), socioeconomic deprivation defined as the most materially disadvantaged fifth of the population (yes, no, unknown), place of residence (rural, urban, unknown), and time period at delivery (1989-1998, 1999-2008, 2009-2019) [15].

Data Analysis

We calculated the rate of necrotizing fasciitis per 100,000 person-years and the cumulative incidence at 31 years of follow-up. We used time-varying Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association of pregnancy complications with risk of necrotizing fasciitis during follow-up. We adjusted the models for age, substance use disorders, socioeconomic deprivation, place of residence, and time period. The time scale was the number of days since first delivery. We accounted for death as a competing outcome using the Fine and Gray method, and censored women who never developed necrotizing fasciitis by the end of study. We examined the proportionality of hazards using survival curves.

In secondary analyses, we assessed the association between pregnancy characteristics and diabetes-related vs. nondiabetic necrotizing fasciitis. We also determined if the association between pregnancy characteristics and necrotizing fasciitis strengthened over time. To do so, we estimated the risk of necrotizing fasciitis by time interval, including 0-4, 5-14, and ≥15 years after the first delivery.

In sensitivity analyses, we analyzed characteristics at the first pregnancy only, as some women do not have subsequent pregnancies. We analyzed the data in SAS v9.4 (SAS Institute Inc., Cary, NC). As we worked with de-identified data, the University of Montreal Hospital Centre's institutional review board waived ethics review.

RESULTS

The cohort included 1,344,996 women with 23,674,870 person-years of follow-up (Table 1). A total of 420 women developed necrotizing fasciitis, including 269 (64.0%) who required intensive care. Group A *Streptococcus* was responsible for 151 cases of necrotizing fasciitis (36.0%) and *Staphylococcus* for 79 cases (18.8%). Diabetes-related necrotizing fasciitis accounted for 83 cases (19.8%). The mean age of women at hospitalization for necrotizing fasciitis was 40.6 years (SD 9.5), and the mean time between delivery and hospitalization was 13.5 years (SD 8.2). Rates of necrotizing fasciitis ranged from 3 to 10 per 100,000 person-years for most pregnancy complications. For women with no pregnancy complication, the rate was 1.1 per 100,000 person-years.

Pregnancy complications were associated with an increased risk of necrotizing fasciitis (Table 2). Compared with no complication, gestational diabetes (HR 1.87, 95% CI 1.38-2.53), cesarean delivery (HR 1.81, 95% CI 1.48-2.21), severe maternal morbidity (HR 2.37, 95% CI 1.70-3.30), multiple birth (HR 2.04, 95% CI 1.29-3.23), preterm birth (HR 2.10, 95% CI 1.65-2.66), and low birth weight (HR 1.84, 95% CI 1.41-2.39) were associated with elevated risks of necrotizing fasciitis. Associations were also present for preeclampsia, placental disorders, postpartum hemorrhage, and neonatal jaundice. Metabolic disorders were associated with 3.72 times (95% CI 2.92-4.74), autoimmune diseases with 2.67 times (95% CI 1.43-5.01), prior infectious disease hospitalizations with 2.69 times (95% CI 2.05-3.54), and kidney diseases with 2.79 times (95% CI 1.69-4.61) the risk of necrotizing fasciitis.

Associations depended on whether necrotizing fasciitis was diabetes-related or not (Table 3). Gestational diabetes (HR 5.15, 95% CI 3.11-8.53), preeclampsia (HR 4.44, 95% CI 2.58-7.64), and preexisting hypertension (HR 8.27, 95% CI 4.40-15.6) were strongly associated with diabetes-related necrotizing fasciitis. Cesarean delivery, severe maternal morbidity, preterm birth, low birth weight, obesity, dyslipidemia, prior infectious disease hospitalization, and kidney disease were associated with both diabetes-related and nondiabetic necrotizing fasciitis. In contrast, placental disorders, postpartum hemorrhage, multiple birth, and immune-related diseases were associated with nondiabetic necrotizing fasciitis.

There was little difference in the incidence of necrotizing fasciitis between exposed and unexposed women in the immediate period after pregnancy (Figure 1). For women with gestational diabetes, preeclampsia, severe maternal morbidity, and preterm birth, the difference in risk of necrotizing fasciitis became more marked 10 to 15 years after delivery. For women with metabolic disorders or prior infectious disease hospitalizations, the difference in risk began to appear 5 years after delivery.

In adjusted regression models, pregnancy complications were more strongly associated with necrotizing fasciitis 5 years or more after delivery (Figure 2). Cesarean section was associated with 1.59 times (95% CI 1.13-2.24), chorioamnionitis with 1.70 times (95% CI 1.01-2.87), preterm birth with 2.36 times (95% CI 1.55-3.60), low birth weight with 1.90 times (95% CI 1.18-3.08), and neonatal jaundice with 1.79 times (95% CI 1.27-2.52) the risk of necrotizing fasciitis 5 to 14 years after pregnancy. Women with metabolic disorders, immune-related disease, prior infectious disease hospitalization, and kidney disease also had an elevated risk of necrotizing fasciitis 5 to 14 years after delivery. Gestational diabetes, preterm birth, metabolic disorders, prior infectious disease hospitalization, and kidney disease remained associated with necrotizing fasciitis 15 years or more after delivery. In contrast, only cesarean section and metabolic disorders were associated with necrotizing fasciitis within 5 years of delivery. In sensitivity analyses, analysis of characteristics at the first pregnancy led to similar findings.

DISCUSSION

In this study of 1.3 million pregnant women with

Table 2. Association Between Pregnancy Characteristics and Risk of Developing Necrotizing Fasciitis

Patient characteristic	Hazard ratio (95% confidence interval)[a]	
	Unadjusted	Adjusted[b]
Pregnancy complication		
Gestational diabetes	2.06 (1.53-2.77)	1.87 (1.38-2.53)
Preeclampsia	1.61 (1.13-2.30)	1.52 (1.07-2.17)
Placental disorder	1.49 (1.11-2.01)	1.41 (1.05-1.90)
Postpartum hemorrhage	1.52 (1.12-2.06)	1.43 (1.06-1.93)
Cesarean section	1.88 (1.54-2.29)	1.81 (1.48-2.21)
Chorioamnionitis	1.23 (0.86-1.75)	1.13 (0.79-1.62)
Severe maternal morbidity	2.51 (1.80-3.50)	2.37 (1.70-3.30)
Intensive care unit admission	5.42 (2.70-10.9)	4.71 (2.34-9.49)
Assisted ventilation	17.8 (5.72-55.7)	14.8 (4.73-46.4)
Severe preeclampsia, eclampsia	2.04 (1.09-3.81)	1.87 (1.00-3.52)
Sepsis	3.52 (1.82-6.82)	3.63 (1.88-7.04)
Surgery-related	2.17 (1.16-4.07)	2.10 (1.12-3.94)
Other severe complication	3.10 (1.70-5.64)	2.76 (1.51-5.03)
Multiple birth	2.12 (1.34-3.36)	2.04 (1.29-3.23)
Preterm birth, <37 weeks	2.21 (1.74-2.81)	2.10 (1.65-2.66)
Low birth weight, <2500 g	1.97 (1.51-2.57)	1.84 (1.41-2.39)
Macrosomia, ≥4000 g	1.03 (0.79-1.35)	1.05 (0.80-1.37)
Neonatal jaundice	1.39 (1.14-1.70)	1.39 (1.13-1.70)
Medical condition		
Metabolic disorder	3.93 (3.08-5.01)	3.72 (2.92-4.74)
Obesity	8.99 (6.52-12.4)	7.14 (5.10-9.99)
Pregestational diabetes	5.84 (4.18-8.17)	5.94 (4.24-8.33)
Preexisting hypertension	2.42 (1.63-3.62)	2.41 (1.62-3.60)
Dyslipidemia	8.79 (3.64-21.3)	7.46 (3.10-17.9)
Immune-related disease	3.00 (1.61-5.62)	2.67 (1.43-5.01)
Prior infectious disease hospitalization	3.13 (2.39-4.09)	2.69 (2.05-3.54)
Kidney disease	3.24 (1.97-5.34)	2.79 (1.69-4.61)

[a]Hazard ratio for gestational diabetes vs. no diabetes, preeclampsia vs. no preeclampsia, and so on. Each pregnancy complication was analyzed separately. [b]Adjusted for age, substance use disorders, socioeconomic deprivation, place of residence, and time period.

three decades of follow-up, we found strong associations between gestational diabetes, preeclampsia, preterm birth, severe maternal morbidity, and other pregnancy complications and the subsequent risk of necrotizing fasciitis. Pregnancy complications were more strongly associated with diabetes-related necrotizing fasciitis, although associations were also present with nondiabetic necrotizing fasciitis. Associations strengthened around 5 years after pregnancy and persisted up to 31 years later. The findings suggest that pregnancy characteristics are markers of later onset of metabolic or immunosuppressive disorders that increase the risk of necrotizing fasciitis in women.

Necrotizing fasciitis is a rare and dangerous infection requiring urgent surgical debridement to prevent mortality [4]. Necrotizing fasciitis is caused by bacteria that penetrate deep fascia after skin trauma, surgery, burns, or other factors compromising the dermal barrier. The extremities are the most common site of infection [4]. There are two types of necrotizing fasciitis: polymicrobial and monomicrobial [18]. Type I, or polymicrobial fasciitis, is caused by aerobic and anaerobic bacteria, and accounts for 80% to 90% of cases [4]. Type II, or monomicrobial fasciitis, is often caused by group A *Streptococcus* or methicillin-resistant *Staphylococcus aureus* [18]. In our

Table 3. Association Between Pregnancy Characteristics and Risk of Diabetes-Related and Nondiabetic Necrotizing Fasciitis

Patient characteristic	Total no. women	Diabetes-related necrotizing fasciitis		Nondiabetic necrotizing fasciitis	
		No. women (N=83)	Hazard ratio (95% confidence interval)[a]	No. women (N=337)	Hazard ratio (95% confidence interval)[a]
Pregnancy complication					
Gestational diabetes	112,735	23	5.15 (3.11-8.53)	25	1.21 (0.81-1.80)
Preeclampsia	76,066	16	4.44 (2.58-7.64)	16	0.94 (0.58-1.53)
Placental disorder	118,736	7	0.90 (0.41-1.96)	41	1.56 (1.13-2.15)
Postpartum hemorrhage	127,913	6	0.96 (0.42-2.20)	40	1.55 (1.12-2.14)
Cesarean section	349,030	40	2.83 (1.83-4.37)	111	1.61 (1.28-2.03)
Chorioamnionitis	104,458	6	1.04 (0.45-2.41)	26	1.16 (0.78-1.71)
Severe maternal morbidity	55,622	13	4.41 (2.45-7.94)	25	1.91 (1.27-2.87)
Intensive care unit admission	6988	<5	10.5 (3.23-34.0)	5	3.56 (1.48-8.58)
Assisted ventilation	819	0	-	<5	18.7 (5.97-58.6)
Severe preeclampsia, eclampsia	19,924	5	5.32 (2.13-13.3)	5	1.14 (0.47-2.76)
Sepsis	7282	5	9.78 (3.97-24.1)	<5	2.04 (0.76-5.48)
Surgery-related	14,907	<5	1.16 (0.16-8.34)	9	2.32 (1.20-4.51)
Other severe complication	15,747	<5	1.38 (0.19-9.97)	10	3.08 (1.64-5.80)
Multiple birth	34,028	<5	1.57 (0.49-4.98)	15	2.17 (1.32-3.59)
Preterm birth, <37 weeks	146,643	19	2.42 (1.47-4.00)	64	2.02 (1.54-2.65)
Low birth weight, <2500 g	122,452	15	2.07 (1.18-3.62)	49	1.78 (1.32-2.41)
Macrosomia, ≥4000 g	196,441	15	1.32 (0.75-2.31)	46	0.99 (0.72-1.34)
Neonatal jaundice	341,855	27	1.41 (0.90-2.22)	110	1.39 (1.10-1.74)
Medical condition					
Metabolic disorder	87,948	42	14.6 (9.47-22.5)	38	2.09 (1.49-2.92)
Obesity	37,568	21	39.1 (22.4-68.4)	21	3.87 (2.47-6.08)
Pregestational diabetes	21,586	31	33.9 (20.6-55.8)	7	1.30 (0.61-2.75)
Preexisting hypertension	34,788	13	8.27 (4.40-15.6)	13	1.42 (0.81-2.48)
Dyslipidemia	2907	<5	26.3 (6.82-101.6)	<5	5.08 (1.62-15.9)
Immune-related disease	16,564	<5	1.48 (0.20-10.8)	8	2.96 (1.52-5.73)
Prior infectious disease hospitalization	88,837	17	4.40 (2.55-7.59)	44	2.34 (1.71-3.22)
Kidney disease	21,097	6	6.59 (2.82-15.4)	9	2.07 (1.10-3.87)

[a]Hazard ratio for gestational diabetes vs. no diabetes, preeclampsia vs. no preeclampsia, and so on, adjusted for age, substance use disorders, socioeconomic deprivation, place of residence, and time period.

study, a third of cases involved group A *Streptococcus* and a fifth involved *Staphylococcus*.

Infection is the most common reason for hospital readmission after pregnancy [19,20]. There is growing evidence that pregnancy complications are associated with severe maternal infections the first year postpartum [7,8]. In a study of 2 million women in the US, postpartum hemorrhage, preterm birth, and cesarean section were associated with two to five times greater odds of readmission for sepsis up to 9 months after pregnancy [7]. A study of 222,751 women found that cesarean delivery was associated with 2.5 times the risk of sepsis or bacteremia 6 weeks postpartum, compared with vaginal delivery [8].

However, risk factors for necrotizing fasciitis are not well understood. Type 2 diabetes is present in up to 60%

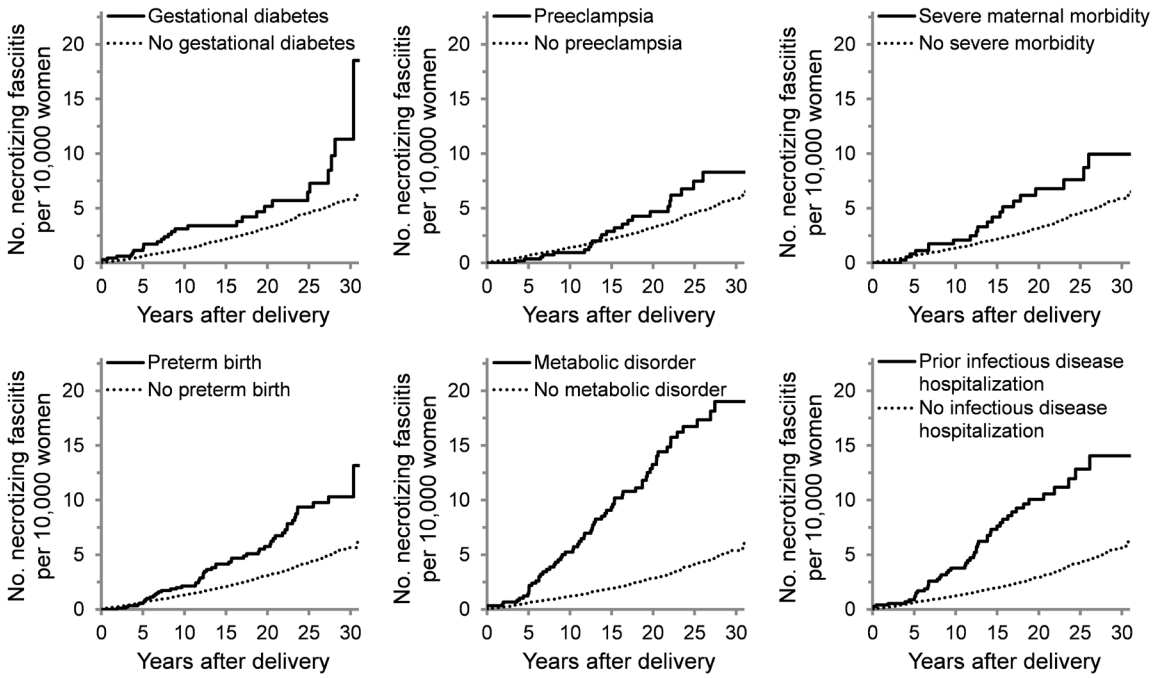

Figure 1. **Cumulative incidence of necrotizing fasciitis over time for selected pregnancy characteristics.**

of cases [4]. Immunocompromised patients are also at greater risk. Smoking, obesity, intravenous drug use, cardiac disease, kidney disease, and age are other risk factors [2-4]. In our study, women with metabolic disorders, immune-related disease, prior infectious disease hospitalizations, and kidney disease all had an elevated long-term risk of necrotizing fasciitis. Nevertheless, data suggest that previously healthy people account for around half of cases of necrotizing fasciitis [4]. For this reason, better documentation of risk factors for necrotizing fasciitis is needed. Pregnancy characteristics may be particularly promising because a growing number of studies suggest that adverse pregnancy outcomes predict chronic disease later in life [21-23].

While researchers have not yet examined the long-term risk of necrotizing fasciitis after pregnancy, a number of studies have assessed the antepartum and postpartum periods [5]. In a study of 4,060,201 women admitted during pregnancy, 148 had necrotizing fasciitis, including 82.4% that occurred postpartum [5]. Only a third of women with necrotizing fasciitis had a chronic comorbidity. A study of 5048 women with cesarean section identified nine cases of polymicrobial necrotizing fasciitis within 2 weeks of delivery [6]. Necrotizing fasciitis after cesarean section is rare, and most data are limited to case reports of otherwise healthy women following surgical complications [24,25]. Our findings suggest that cesarean delivery is also associated with necrotizing fasciitis after the postpartum period.

In this study, women with gestational diabetes, preeclampsia, and other adverse outcomes all had an elevated risk of necrotizing fasciitis in the long term. Many of these pregnancy outcomes are associated with the development of known risk factors for necrotizing fasciitis, such as type 2 diabetes and obesity. Gestational diabetes is associated with 7 times and preeclampsia with 2 times the risk of developing type 2 diabetes after pregnancy [12,13]. In our data, associations were more pronounced 5 years after delivery, supporting the possibility that pregnancy complications are an early sign of long-term metabolic disorders that increase the risk of necrotizing fasciitis later on. Gestational diabetes and preeclampsia are also associated with cesarean section and preterm delivery [23,26], other complications we found were associated with necrotizing fasciitis.

A related issue is that we could not adjust for all confounders, as necrotizing fasciitis was rare and pregnancy complications were too numerous to include in one time-varying model. Pregnancy complications may be correlated or share metabolic pathways. Preterm birth, low birth weight, preeclampsia, and other pregnancy complications frequently coincide. Metabolic disorders are involved in a range of pregnancy complications, including preeclampsia, gestational diabetes, preterm birth, and cesarean section [27-29], all of which were associated with necrotizing fasciitis in our study. Up to 24% of pregnancy complications are attributable to overweight and obesity [27]. Future studies with larger numbers of patients with necrotizing fasciitis will be needed to disentangle the effects of interrelated pregnancy complications.

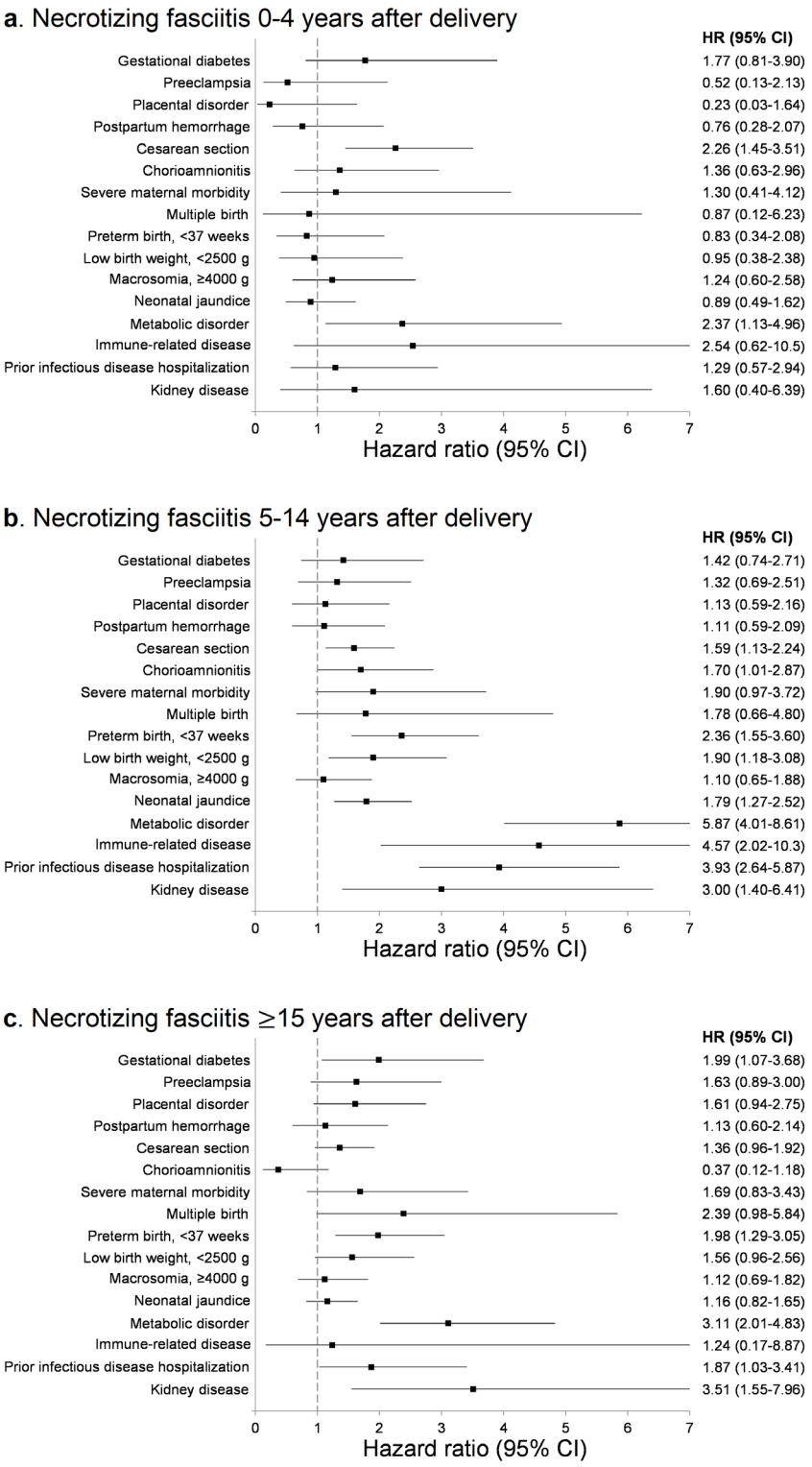

Figure 2. **Change in the association between pregnancy characteristics and risk of necrotizing fasciitis over time.** Association of pregnancy characteristics with necrotizing fasciitis at (**a**) 0 to 4 years (N=79), (**b**) 5 to 14 years (N=158), and (**c**) ≥15 years after delivery (N=183). These cutpoints are meant to reflect short, medium, and long-term risks of necrotizing fasciitis after pregnancy. Hazard ratios are for gestational diabetes vs. no diabetes, preeclampsia vs. no preeclampsia, and so on, adjusted for age, substance use disorders, socioeconomic deprivation, place of residence, and time period.

Nonmetabolic or immune pathways may also be involved, as many women had nondiabetic necrotizing fasciitis in this study. Women with placental disorders, postpartum hemorrhage, severe maternal morbidity, multiple birth, and neonatal jaundice all had elevated risks of nondiabetic necrotizing fasciitis. While some of these pregnancy complications may be linked with immunosuppressive disorders, this pathway is not immediately apparent for conditions such as postpartum hemorrhage and placental disorders. Further research is warranted to identify pathways that may explain the associations.

The risk of necrotizing fasciitis may be modulated by predisposing risk factors such as socioeconomic status or race and ethnicity. We were able to adjust for socioeconomic deprivation but did not have data on race and ethnicity in this study. A 6-year retrospective review of 130 patients from Manitoba found that the incidence of necrotizing fasciitis was higher in the Aboriginal population than other individuals [30]. While there is a paucity of studies on the role of race and ethnicity in necrotizing fasciitis, there is some evidence of an association with outcomes such as sepsis. A study of 10 million patients in the United States found that the incidence of sepsis was higher among non-white patients, and that mortality was greatest for Black men [31]. Although we did not have information on race and ethnicity, Quebec is multicultural, and the results are likely representative of areas with racial diversity.

This study had other limitations. We could not investigate rare pregnancy complications due to the limited number of women with necrotizing fasciitis. We had 80% power to detect an odds ratio of 1.71 and 90% power for an odds ratio of 1.86, assuming a prevalence of 4 pregnancy complications per 100 women, 4 cases of necrotizing fasciitis per 10,000 exposed women, and a 2-tailed α=0.05 [32]. We could not differentiate polymicrobial from monomicrobial fasciitis and lacked information on infection severity. Residual confounding may be present due to underreporting of substance use disorders. Potential confounders such as immunosuppressive drugs were not available. We used hospital data and cannot rule out misclassification of variables due to coding errors. We could not determine the reason for cesarean delivery or the extent to which pregnancy complications predict risk factors in the path to necrotizing fasciitis, although we were able to identify nondiabetic necrotizing fasciitis. The findings apply to a population with publicly funded healthcare, but generalizability to regions with different healthcare delivery models is to be determined.

The overall message conveyed by this study is that gestational diabetes, preeclampsia, and other adverse pregnancy outcomes may be predictors of rare infectious diseases later in life, most likely due to intervening diabetes, obesity, or other immunosuppressive conditions. Women with complications during pregnancy are considered at risk of cardiovascular disease and encouraged to adopt preventative health behaviors [21-23]. However, these benefits could also extend to the prevention of serious infectious diseases, including necrotizing fasciitis. Prevention of harmful infectious diseases may begin early in life for women who experience pregnancy complications.

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Appendix A

Figure S1 Criteria for study inclusion and exclusion

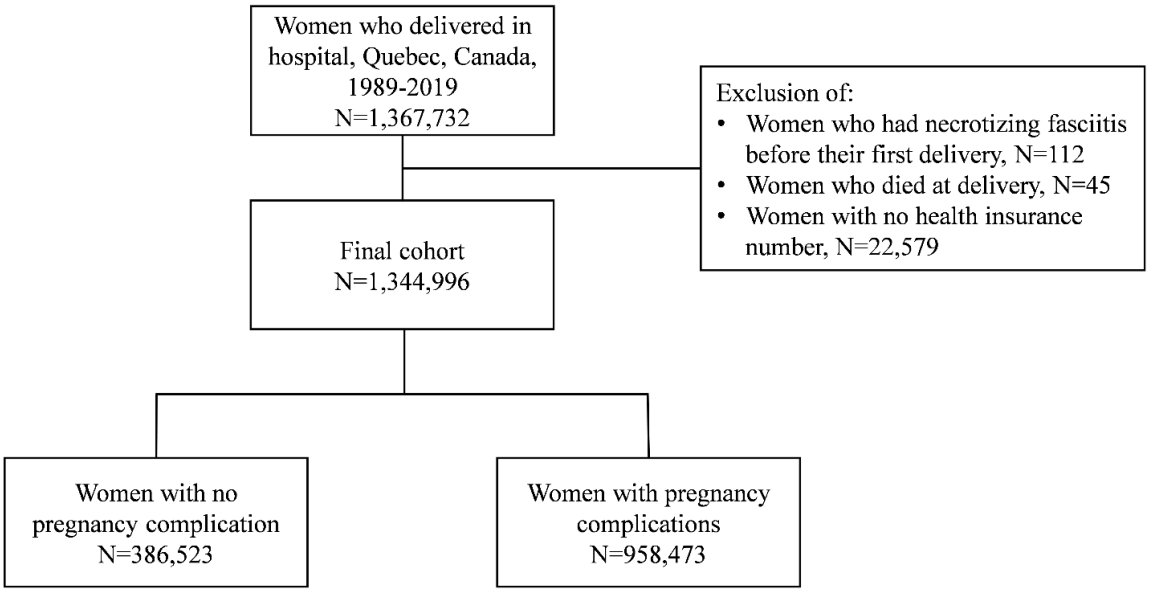

Table S1 Diagnostic and procedure codes for pregnancy characteristics and necrotizing fasciitis

Patient characteristic	International Classification of Diseases-9 / Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (before 2006)	International Classification of Diseases-10 / Canadian Classification of Health Interventions (beginning in 2006)
Pregnancy complication		
Gestational diabetes	648.8, V12.21	O24.8
Preeclampsia	642.4-642.7	O11, O13-O15
Placental disorder[a]	641.0-641.2, 656.7, 667, 762.0	O43.2, O43.81, O44, O45, O73, P02.0
Postpartum hemorrhage	666	O72
Cesarean section	86.0-86.2, 86.8, 86.9	5.MD.60
Chorioamnionitis	658.4, 762.7	O41.1, P02.7
Severe maternal morbidity	Codes published by Dzakpasu et al[b]	Codes published by Dzakpasu et al[b]
Multiple birth	yes/no	yes/no
Preterm birth	<37 weeks gestation	<37 weeks gestation
Low birth weight	<2500 g	<2500 g
Fetal macrosomia	≥4000 g	≥4000 g
Neonatal jaundice	774/13.82	P57.8, P57.9, P58, P59/1.YZ.12.JA-DQ
Medical condition		
Metabolic disorder	401-405, 249, 250, 272, 278.0, 642.0-642.2,642.9, 646.2, 648.0, 649.1, V77.8	E10-E14, E66, E78, I10-I15, O10, O24.5-O24.7
Obesity	278.0, 649.1, V77.8	E66
Pregestational diabetes	249, 250, 648.0	E10-E14, O24.5-O24.7
Preexisting hypertension	401-405, 642.0-642.2, 642.9, 646.2	I10-I15, O10
Dyslipidemia	272	E78
Immune-related disease	136.1, 242.0, 245.2, 258.1, 273.2, 279.49, 283.0, 286.52, 287.0, 287.32, 289.81, 340, 357.0, 358.0, 358.3, 370.52, 446.0-446.2, 446.4, 446.5, 446.7, 555, 556, 571.42, 579.0, 581.2, 582.2, 583.2, 616.51, 694.0, 694.2, 694.4-694.6, 696.0, 696.1, 711.2, 714, 704.01, 709.01, 710.0-710.2, 720	D59.0, D59.1, D68.6, D69.0, D69.30, D89.1, E05.0, E06.3, E31.0, G35, G61.0, G70.0, G73.1, H16.3, K50, K51, K75.4, K90.0, L10, L12, L13.0, L40, L63, L80, M06, M07.0-M07.3, M09.0, M30.0, M30.1, M30.3, M30.8, M31.0, M31.3-M31.8, M32, M34.0, M34.1, M34.8, M34.9, M35.0, M35.2, M35.9, M45, N77.8
Prior infectious disease hospitalization	001-139	A00-B99
Kidney disease	580-591, 592.0, 593.0-593.2, 593.81, 593.9	N00-N13.3, N13.6, N14-N20.0, N20.2, N25-N28.1, N28.80, N28.82, N28.9
Necrotizing fasciitis	728.86	M72.6
Diabetes-related	728.86 with 249 or 250	M72.6 with E10-E14
Nondiabetic	728.86 without 249 or 250	M72.6 without E10-E14

[a]Placenta abruption, accreta, previa, infarction, retention. [b]Dzakpasu S, Deb-Rinker P, Arbour L, Darling EK, Kramer MS, Liu S, et al. Severe maternal morbidity surveillance: Monitoring pregnant women at high risk for prolonged hospitalization and death. Paediatr Perinat Epidemiol. 2020;34(4):427–439.