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Effect of peripartum *Clostridioides difficile* infection on pregnancy and neonatal outcomes: an observational study

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Abstract

Background: The incidence of *Clostridioides difficile* infection (CDI) in peripartum women is rising, but limited data on its effect on maternal and neonatal outcomes are available.

Objective: To study the effect of peripartum CDI on pregnancy and neonatal outcomes.

Design: Retrospective cohort study.

Methods: Patients with peripartum CDI 12 weeks before pregnancy through 6 weeks postpartum (January 1996–February 2018) were matched with controls (peripartum women without CDI) 1:1 by age, year of delivery, and prior pregnancies. McNemar's test and conditional logistic regression were used to analyze the effect of CDI on pregnancy and neonatal outcomes (complications, mode of delivery). $p < 0.05$ was considered statistically significant.

Results: Overall, 101 cases and 100 controls (1997–2018) were included; median age 27 (range, 20–41) years. Timing of CDI was as follows: pre-pregnancy: 15.8% ($n = 16$), during pregnancy: 51.5% ($n = 52$), and postpartum: 32.7% ($n = 33$). The commonest risk factor was outpatient/emergency room visits. Pregnancy and neonatal outcomes were analyzed for 67 matched pairs with CDI before or during pregnancy. Cases had higher odds of cesarean delivery ($p = 0.02$) and lower odds of Group B *Streptococcus* (GBS) infection/colonization ($p = 0.03$). Odds of cesarean delivery remained high after controlling for labor arrest disorders [odds ratio (OR): 17.23 (95% confidence interval (CI), 2.19–543.19; $p = 0.004$)]; odds of GBS remained low after controlling for antibiotic use (OR: 0.25, 95% CI, 0.04–0.99; $p = 0.049$). Neonatal outcomes were similar in cases and controls. CDI treatment did not affect treatment-related or delivery outcomes.

Conclusion: Peripartum CDI was associated with higher odds of cesarean delivery and lower odds of GBS infections. Larger studies exploring the effect of CDI on pregnancy and neonatal outcomes are needed.

Keywords: antibiotic, children, diarrhea, FMT, infection, microbiome obstetric, microbiota transplant, pediatric

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Introduction

Clostridioides difficile infection (CDI) is the most common healthcare-associated (HA) infection in the United States with increasing incidence in younger patients and community dwellers.[1] Patients with CDI have significant morbidity and are at risk for complications such as hypotension, sepsis, colonic perforation, and even death. Traditionally, peripartum women were considered at low risk for contracting CDI, although recent reports have documented a twofold increase in the incidence in this population.[2,3]

Despite being a highly vulnerable patient population, data on the effect of CDI on pregnancy and associated outcomes remain scarce. One study using the National Inpatient Sample database found increased risk of adverse maternal outcomes with CDI complicating delivery admissions.[2] The adverse outcomes included longer hospital stays, higher risk of venous thromboembolism, paralytic ileus, sepsis, and death. In another study, women who contracted CDI in the immediate peripartum period more often experienced complications such as postpartum endometritis, chorioamnionitis, and need for cesarean delivery.[8] To our knowledge, no studies have explored the effect of peripartum CDI on neonatal outcomes.

We conducted a retrospective study exploring the effect of peripartum CDI on pregnancy and neonatal outcomes. We also studied CDI-related outcomes in this patient population.

Materials and methods

Study population

Peripartum women at Mayo Clinic (1 January 1996–28 February 2018) and who authorized the use of their medical information for research were eligible for inclusion. CDI and pregnancy diagnosis codes were used to identify cases and controls; medical records were reviewed to confirm eligibility. Cases were patients with definite CDI within 12 weeks before pregnancy, during pregnancy, or in the 6 weeks postpartum (see Supplemental Table S1 for definitions). CDI during any of these time periods was considered 'peripartum CDI'. Controls were pregnant women without peripartum CDI. Cases and controls were matched by year of delivery (within 5 years of each other), age and gravidity (number of pregnancies); one control was randomly selected from the potential matches for each case. The study was consistent with STROBE guidelines (Supplemental Table S2).[4]

Data collection

Data were abstracted from medical records, collected and managed using REDcap.[5] Records within and from outside our healthcare system (where authorization was given to access charts) were used to collect data. Cases and controls were followed throughout their pregnancy until 6 weeks postpartum for obstetric outcomes. For outcomes related to CDI, cases were followed up to 1 year after CDI. Demographics, details about current *C. difficile* episode [known CDI risk factors within 90 days prior, severity, treatment, complications, treatment-related adverse events (AEs), recurrences (within 56 days) and future CDI episodes (within 1 year)] were collected. Details of current and prior pregnancies including obstetric and neonatal (up to 28 days of age) complications were recorded. All diagnoses were as documented in the patient's record by the treating physician. For cases, only complications that occurred after the CDI episode were included. Timing of complications in pregnancy was recorded.

Neonatal birthweight and complications were abstracted from medical records of the neonate or the mother as per availability. In case of multiple births, the neonate with the worst outcome was selected, as the limited number of such events precluded more advanced analyses.

Outcomes assessed

Primary outcome was the effect of CDI on pregnancy (obstetric complications, gestational period at delivery, mode of delivery – cesarean *versus* vaginal). Secondary outcomes included effect of CDI on birth weight and neonatal complications, and CDI-related outcomes (complications, treatment response, treatment-related AEs in mother and neonate, recurrences).

Effect of CDI on obstetric complications was studied separately for patients with antenatal CDI (CDI before or during pregnancy) and postpartum CDI. To analyze the effect of CDI on pregnancy and neonatal outcomes, only cases with antenatal CDI (and their corresponding controls) were included. To study the effect of postpartum CDI on postpartum obstetric complications, cases with CDI in the postpartum period along with their corresponding controls were included. In patients with antenatal CDI, we separately reported outcomes for patients with pre-pregnancy CDI and those with CDI during pregnancy.

Statistical analysis

Descriptive statistics were used for baseline characteristics, details of CDI, and pregnancy. Wilcoxon test for continuous variables, chi

square/Fischer's exact test for categorical variables were used as applicable for analyzing unmatched data.

Matched pair analysis using McNemar's test (or McNemar's test using exact binomial probability calculations http://vassarstats.net/propcorr.html) was done to analyze the effect of CDI on pregnancy and neonatal outcomes. Multivariable conditional logistic regression was used to analyze the effect of CDI on obstetric outcomes. To study the association of CDI with cesarean delivery, a common risk factor for cesarean delivery (labor arrest disorders) was included in the regression model.[6] Elective or planned cesarean deliveries were excluded from this analysis. Other risk factors for cesarean delivery such as fetal malpresentation or other maternal/fetal indications were not included in the regression model due to limited number of events. To study the effect of CDI on Group B *Streptococcus* (GBS) infection/colonization, prior antibiotic use during pregnancy was included as a variable in the regression model. Similar matched analyses were done to assess the effect of postpartum CDI on postpartum complications. All matched analyses were subcategorized based on timing of CDI during pregnancy.

Multivariable logistic regression was used to study the effect of CDI risk factors and timing (during pregnancy) on severity (severe or fulminant CDI *versus* mild–moderate CDI). Variables were included in the model if they were significant at the 10% level in univariate analysis. For all analyses, a two-tailed p value of <0.05 was considered as statistically significant. JMP® Pro 14.1.0 © 2018 SAS was used for statistical analysis.

Results

Patient demographics

A total of 101 cases and 100 matched controls from 1997 to 2018 were included (Supplemental Figure 1); one patient did not have data on gravidity, hence could not be matched. Median age was 27 years (range, 20–41 years); baseline characteristics are given in Table 1. Timing of CDI was as follows: pre-pregnancy, 15.8% (16); during pregnancy, 51.5% (52) [1st trimester, 17.8% (18), 2nd trimester, 21.7% (22); and 3rd trimester, 11.9% (12)], and postpartum, 32.7% (33).

Effect of CDI on pregnancy and neonatal outcomes

Of all patients, 68 cases and 67 controls had antenatal CDI. Data for delivery outcomes were available in 63 cases and 66 controls. Pregnancy and neonatal outcomes were analyzed for the 67 matched pairs with antenatal CDI (Tables 2–4). On univariate analysis, cases were more likely than controls to undergo cesarean delivery and had lower odds of GBS infection/colonization (Tables 2 and 3). On multivariable conditional logistic regression, after controlling for labor arrest disorders, the odds of cesarean delivery were higher in cases than controls (OR: 17.23, 95% CI, 2.19–543.19; $p=0.004$). Controlling for antibiotic use, the odds for GBS infection remained low (OR: 0.25, 95% CI, 0.04–0.99; $p=0.049$). The odds of cesarean delivery were higher, and the odds of GBS infections were lower in patients with CDI during pregnancy, but not with CDI in the pre-pregnancy period (Tables 2 and 3).

As maternal and neonatal medical records are not routinely linked, data for several neonates were unavailable. Of the 54 documented live births in cases (of the 68 total cases: 9 had an abortion and 5 had no data on delivery outcome), data on neonatal complications and birthweight were available in 74.1% (40) and 85.2% (46) cases, respectively. Similarly, of the 57 controls with documented live births (of the 67 total controls: 9 had an abortion and 1 had no data on delivery outcome), data on neonatal complications and birthweight were available in 73.7% (42) and 82.5% (47), respectively. Of the patients with available information, neonatal outcomes were similar amongst cases and controls (Table 4).

Effect of postpartum CDI on obstetric complications

CDI in the postpartum period was not associated with higher odds of postpartum complications (mastitis, vaginitis, GBS infection/colonization, abscess at any site; $p>0.05$).

Characteristics of peripartum CDI

According to the definitions provided in Supplemental Table S1, most cases [41.6% (42)] were HA [of these, 73.8% (31) were community onset and 26.2% (11) were healthcare facility onset], 38.6% (39) were community associated

Table 1. Baseline characteristics and pregnancy history.

Characteristics*		Cases ($n=101$)	Controls ($n=100$)	p Value
Age		27 (20–41)	28 (20–42)	0.23
Advanced maternal age (>35 years)		11.9%	13.0%	0.81
Prior pregnancies (parity)		1 (0–5)	1 (0–4)	0.37
Prior abortions		0 (0–5)	0 (0–4)	0.30
Prior vaginal deliveries		36.6%	47.0%	0.14
Prior cesarean deliveries		13.9%	16.0%	0.67
Number of prior cesarean deliveries		1.5 (1–3)	1.5 (1–3)	0.98
Obstetrical complications in prior pregnancies		41.5%	32.8%	0.34
Race	White	92.1%	91.0%	0.93
	African American	2.9%	2.0%	
	Asian	1.9%	3.0%	
	American Indian/Alaskan	0	1.0%	
	Other	0.9%	2.0%	
	Unknown/not reported	1.9%	1.0%	

*Data are given as median (min-max) for continuous variables, percentages for categorical variables.

(CA), 11.9% (12) were indeterminate, and 7.9% (8) were unknown. Among the known risk factors for CDI, the most common risk factor observed was outpatient or emergency room visit (Supplemental Table S3). Median number of antibiotics received prior to CDI was 2 (range: 1–6). Five patients had prior CDI episodes, median 38 (range: 14–64) weeks prior to the current episode. Interestingly, 43.6% (17) of CA-CDI cases did not have prior antibiotic exposure, while 5.1% (2) had none of the usual risk factors. Majority (68.7%) had mild–moderate CDI, 22.2% had severe CDI, 9.1% had fulminant CDI; two patients did not have sufficient data (Supplemental Table S3).

CDI-related outcomes

CDI-related complications were shock (8 patients; 1 pre-pregnancy, 3 during pregnancy, 4 postpartum), sepsis (4 patients; 1 during pregnancy, 3 postpartum), ICU admission (3 patients; 1 during pregnancy, 2 postpartum), and colectomy (2 patients; 1 during pregnancy, 1 postpartum).

On univariate analysis, there was higher odds of severe/fulminant disease in CDI during pregnancy and postpartum compared to pre-pregnancy CDI. Similarly, the odds were higher in HA *versus* CA CDI, and in patients with CDI risk factors: hospitalization, prior antibiotics, prior surgery ($p<0.05$ for all). On multivariable logistic regression, prior surgery (OR: 3.98, 95% CI, 1.52–10.47; $p=0.005$) and antibiotic use (OR: 3.49, 95% CI, 1.18–10.34; $p=0.02$) were associated with severe/fulminant CDI.

Treatment of CDI. The most common initial treatment was metronidazole in 66.3% (65), followed by vancomycin standard regimen in 29.6% (29) of patients (Supplemental Figure 2(a), Supplemental Table S4). Choice of antibiotic did not affect treatment-related or delivery outcomes (Supplemental Table S5).

Overall, 24.7% (24) of patients needed a change in treatment (metronidazole *versus* vancomycin: $p=0.39$). Of these, 17 were due to non-resolution of diarrhea and 7 due to AEs. Subsequent treatment and response are shown in Supplemental

Table 2. Association of antenatal CDI with pregnancy outcomes.*

Pregnancy outcome	All cases				Pre-pregnancy CDI cases				During pregnancy CDI cases			
	Cases (*N* = 68) % (*n*)	Controls (*N* = 67) % (*n*)	Odds ratio (95% CI)[$]	*p* Value	Cases (*N* = 16) % (*n*)	Controls (*N* = 16) % (*n*)	Odds ratio (95% CI)[$]	*p* Value	Cases (*N* = 52) % (*n*)	Controls (*N* = 51) % (*n*)	Odds ratio (95% CI)[$]	*p* Value
Live birth	86.9 (53)	88.5 (54)	0.85 (0.29–2.55)	0.78	68.8 (11)	93.8 (15)	0.2 (0.02–1.7)	0.22	93.3 (42)	86.7 (39)	2.5 (0.48–12.88)	0.45
Spontaneous abortion	9.8 (6)	9.8 (6)	1.0 (0.29–3.45)	1.0	25.0 (4)	6.3 (1)	4 (0.45–35.8)	0.38	4.4 (2)	11.1 (5)	0.25 (0.03–2.23)	0.37
Cesarean[‡]	26.5 (13)	10.2 (5)	9.0 (1.14–71.04)	0.02	20.0 (2)	10.0 (1)	–	1.0	28.2 (11)	10.3 (4)	8.0 (1.0–63.9)	0.04
Preterm birth	8.3 (5)	5.0 (3)	1.67 (0.39–6.97)	0.72	13.3 (2)	0 (0)	–	–	6.7 (3)	6.7 (3)	1.0 (0.2–4.9)	1.0
Post-term birth	8.3 (5)	6.7 (4)	1.25 (0.34–4.65)	1.0	6.7 (1)	20.0 (3)	0.33 (0.03–3.2)	0.63	8.9 (4)	2.2 (1)	4 (0.45–35.8)	0.38

Data are represented as the percent of cases and controls who had the outcome among the matched pairs analyzed. Pairs with missing data were excluded from the analysis.
*Excluding cases with postpartum CDI.
[$]Odds ratio are calculated using data from discordant pairs only.
[‡]After excluding patients who underwent an elective or repeat cesarean section.
CDI, *Clostridioides difficile* infection.

Table 3. Association of antenatal CDI with obstetric complications.*

Complication	All cases				Pre-pregnancy CDI cases				During pregnancy CDI cases			
	Cases % (*n*)	Controls % (*n*)	Odds ratio (95% CI)$	*p* Value	Cases % (*n*)	Controls % (*n*)	Odds ratio (95% CI)$	*p* Value	Cases % (*n*)	Controls % (*n*)	Odds ratio (95% CI)$	*p* Value
Vomiting in pregnancy/ hyperemesis gravidarum	13.4 (9)	2.9 (2)	4.5 (0.97–20.83)	*0.07*	*12.5 (2)*	*6.3 (1)*	2.0 (0.18–22.06)	1.0	*13.7 (7)*	*1.9 (1)*	*7 (0.86–56.89)*	*0.07*
GBS colonization/ infection	7.5 (5)	23.9 (16)	0.31 (0.11–0.85)	0.03‡	6.3 (1)	18.8 (3)	0.33 (0.03–3.2)	0.63	7.8 (4)	25.5 (13)	0.31 (0.10–0.94)	0.049‡
Venous thrombosis	2.9 (2)	1.5 (1)	2 (0.18–22.06)	1.0	6.3 (1)	6.3 (1)	1.0 (0.06–15.98)	1.0	1.9 (1)	0 (0)	–	–
Anemia	17.9 (12)	19.4 (13)	0.9 (0.37–2.21)	0.82	18.8 (3)	25.0 (4)	0.75 (0.17–3.35)	1.0	17.6 (9)	17.6 (9)	1.0 (0.32–3.1)	1.0
Urinary tract infection	11.9 (8)	8.9 (6)	1.33 (0.46–3.84)	0.59	18.8 (3)	12.5 (2)	1.5 (0.25–8.97)	1.0	9.8 (5)	7.8 (4)	1.25 (0.33–4.66)	1.0
Vaginal bleeding antepartum	5.9 (4)	4.5 (3)	1.5 (0.25–8.98)	1.0	12.5 (2)	0 (0)	–	–	3.9 (2)	5.9 (3)	0.5 (0.05–5.5)	1.0
Non-reassuring fetal heart rate/rhythm	13.4 (9)	5.9 (4)	2.25 (0.69–7.30)	0.27	6.3 (1)	12.5 (2)	0.5 (0.05–5.51)	1.0	15.7 (8)	3.9 (2)	4 (0.85–18.84)	0.11
Preterm labor	8.9 (6)	2.9 (2)	5 (0.58–42.79)	0.22	0 (0)	0 (0)	–	–	11.7 (6)	3.9 (2)	5 (0.58–42.78)	0.22
Gestational hypertension	8.9 (6)	2.9 (2)	5 (0.58–42.79)	0.22	18.8 (3)	6.3 (1)	–	0.5	5.9 (3)	1.9 (1)	3 (0.31–28.84)	0.63
Threatened abortion	4.5 (3)	4.5 (3)	1.0 (0.20–4.95)	1.0	6.3 (1)	0 (0)	–	–	3.9 (2)	5.9 (3)	0.67 (0.11–3.98)	1.0
Pre-eclampsia	2.9 (2)	4.5 (3)	0.67 (0.11–3.98)	1.0	6.3 (1)	0 (0)	–	–	1.9 (1)	5.9 (3)	0.33 (0.03–3.2)	0.63
Gestational diabetes	2.9 (2)	2.9 (2)	1.0 (0.14–7.09)	1.0	0 (0)	12.5 (2)	–	–	3.9 (2)	0 (0)	–	–
Bacterial vaginosis	1.5 (1)	5.9 (4)	0.25 (0.03–2.24)	0.37	6.3 (1)	6.3 (1)	1.0 (0.06–15.98)	1.0	0 (0)	5.9 (3)	–	–
Fetal growth restriction	1.5 (1)	1.5 (1)	1 (0.06–15.98)	1.0	6.3 (1)	0 (0)	–	–	0 (0)	1.9 (1)	–	–
MRSA colonization/ infection	1.5 (1)	1.5 (1)	1 (0.06–15.98)	1.0	0 (0)	0 (0)	–	–	1.9 (1)	1.9 (1)	1.0 (0.06–15.98)	1.0
Weight loss	20.1 (10)	20.1 (10)	1 (0.35–2.85)	1.0	33.3 (4)	25.0 (3)	0.5 (0.18–22.05)	1.0	16.7 (6)	29.4 (7)	0.83 (0.25–2.73)	1.0

Data are represented as the percent of cases and controls who had the outcome among the matched pairs analyzed. Pairs with missing data were excluded from the analysis.
*For all complications, temporality (occurrence of complication after CDI episode) was confirmed.
$Odds ratios are calculated from discordant pairs only.
p Values significant at 5% are marked in '‡'; *p* Values significant at 10% level are *italicized*.
CDI, Clostridioides difficile infection; GBS, Group B *streptococcus*; MRSA, Methicillin-resistant *Staphylococcus aureus*.

Table 4. Association of maternal antenatal CDI with neonatal outcomes.

Complication	All cases				Pre-pregnancy CDI cases				During pregnancy CDI cases			
	Cases % (*n*)	Controls % (*n*)	Odds ratio (95% CI)	*p* Value	Cases % (*n*)	Controls % (*n*)	Odds ratio (95% CI)	*p* Value	Cases % (*n*)	Controls % (*n*)	Odds ratio (95% CI)	*p* Value
Low birth weight	5.7 (2)	2.9 (1)	2.0 (0.18–22.06)	1.0	0 (0)	0 (0)	–	–	7.1 (2)	3.6 (1)	2.0 (0.18–22.06)	1.0
Macrosomia	5.7 (2)	8.6 (3)	0.67 (0.11–3.99)	1.0	0 (0)	0 (0)	–	–	7.1 (2)	10.7 (3)	0.67 (0.11–3.99)	1.0
Fever/possible sepsis	7.1 (2)	3.6 (1)	2.0 (0.18–22.06)	1.0	0 (0)	0 (0)	–	–	9.1 (2)	4.6 (1)	2.0 (0.18–22.06)	1.0
Any infection	10.7 (3)	14.3 (4)	0.75 (0.17–3.35)	1.0	16.7 (1)	0 (0)	–	–	9.1 (2)	18.2 (4)	0.5 (0.09–2.73)	0.69
Jaundice	17.9 (5)	39.3 (11)	0.86 (0.29–2.55)	0.78	0 (0)	16.7 (1)	–	–	22.7 (5)	45.5 (10)	0.38 (0.09–1.41)	0.23
Respiratory distress	14.3 (4)	0 (0)	*	0.12	16.7 (1)	0 (0)	–	–	13.6 (3)	0 (0)	–	0.25
Hypoglycemia	7.1 (2)	3.6 (1)	2.0 (0.18–22.06)	1.0	16.7 (1)	0 (0)	–	1.0	4.6 (1)	4.6 (1)	1.0 (0.06–15.99)	1.0
Candida infection	3.6 (1)	3.6 (1)	1.0 (0.06–15.99)	1.0	16.7 (1)	0		–	0	4.6 (1)		–

Data are represented as the percent of cases and controls who had the outcome amongst the matched pairs analyzed. Pairs with missing data were excluded from the analysis.
*OR could not calculated because the denominator in McNemar's OR (number of matched pairs with outcome of case = negative, and outcome of control = positive) was zero.
CDI, *Clostridioides difficile* infection; CI, confidence interval.

Figure 2. Overall, 3.1% (3) of patients were refractory to all antibiotics; one underwent fecal microbiota transplantation (FMT) after receiving fidaxomicin and two underwent colectomy.

Recurrent CDI (within 56 days of treatment completion) occurred in 11.1% (11) patients; median number of recurrences 2 (range: 1–3). Five patients underwent FMT for recurrent CDI. Thus, six patients in total underwent FMT, one in the 2nd trimester, one in the 3rd trimester, and four in the postpartum period. No patient underwent a repeat FMT. All FMTs were performed *via* colonoscopy. Four patients received moderate sedation with midazolam and fentanyl, while two received anesthesia with propofol (1), propofol and ketamine (1). Of the two patients receiving anesthesia assisted sedation, one patient was in the 2nd trimester of pregnancy, while the other was in the postpartum period. Of the patients undergoing FMT during pregnancy, one had data on neonatal outcomes, and there were no complications noted.

Safety of CDI treatment. Overall, AEs were reported due to metronidazole in 14 patients, due to vancomycin in five patients and due to FMT in five patients. The most common AE was nausea (Supplemental Table S6). There was one serious AE due to metronidazole (anaphylaxis). One patient had preterm contractions without preterm delivery 3 weeks following FMT, which was deemed unlikely to be related to FMT. No neonate experienced an AE attributed to treatment in the mother. There were no CDI- or pregnancy-related deaths.

Discussion

In this retrospective study, peripartum women with CDI had higher odds of primary cesarean delivery and lower odds of GBS infection than controls. CDI was primarily HA, and outpatient/emergency room visits were the commonest risk factor. Metronidazole was the commonest CDI treatment; choice of treatment did not affect treatment-related or delivery outcomes. Peripartum CDI did not affect neonatal outcomes. Minor treatment-related AEs were common; six patients received FMT and tolerated it well.

Several reports of peripartum CDI have emerged recently.[2,3,7,8] In a study using a national database, peripartum women with CDI had higher risk of adverse outcomes (sepsis, paralytic ileus, venous thromboembolism, longer hospital stay, death) than controls.[2] The study looked at women admitted for delivery; thus, CDI earlier in pregnancy and in the postpartum period would not be included. It is possible that the proportion of patients with severe CDI was higher than our study, though markers of severity are not captured by administrative databases. Our study included inpatient and outpatients with CDI anytime during pregnancy or postpartum, with most patients having mild–moderate disease. This could partly account for the differences in outcomes. In our study, the differing risk of cesarean delivery and GBS infections were significant only in CDI occurring during pregnancy. This could suggest that CDI affects outcomes in the immediate time following the infection, without having long-term effects. Interestingly, the low risk of GBS infection persisted after controlling for antibiotic use. Frequent healthcare contact in cases leading to better utilization of antenatal care could account for these results.

A study in 20 women with peripartum CDI (4 weeks before/after delivery) found that cesarean delivery, postpartum endometritis, and chorioamnionitis were more frequent in cases *versus* controls (80 pregnant women without CDI).[8] Temporality of CDI with respect to obstetric complications was not specified; thus, attributable effect of CDI on outcomes is difficult to establish.

In our study, most cases were HA-CDI; the proportion of CA-CDI was comparable to the general population.[9,10] Most patients had healthcare contact prior to CDI; conceivably several of these visits were part of antenatal care. Future studies should explore the frequency of healthcare exposure as a risk factor for CDI.

Metronidazole was the commonest treatment given for CDI. Metronidazole crosses the placenta and has high concentrations in breastmilk; previous studies have raised safety concerns with the drug in pregnant and lactating women.[11–14] There are no similar pharmacokinetic studies of oral vancomycin or fidaxomicin. However, due to low systemic absorption, these drugs are unlikely to be present in significant concentrations in breastmilk or cord blood.[15,16] Recent guidelines recommend vancomycin or

fidaxomicin as first-line treatments for CDI owing to their superior efficacy and safety profile.[9] Our study reports the largest number of cases of FMT in peripartum women to date, with no serious AEs. In a previous case report, a patient with multiply recurrent CDI received FMT in her second trimester with no serious AEs.[17] Our study indicates FMT is well tolerated in pregnancy and adds to the limited body of evidence on safety of FMT in peripartum women.

To our knowledge, this is the largest single-center study looking at peripartum CDI, and the first to study its effect on both pregnancy and neonatal outcomes. Strengths of the study are the inclusion of inpatients and outpatients, matched study design, follow-up of each subject through pregnancy and postpartum period, and manual review of medical records. Temporality of complications with respect to CDI was confirmed, increasing our confidence in the results. Limitations of the study include the possibility of residual confounding, incomplete data for neonates due to non-linkage of maternal and neonatal records, and lack of information on ribotyping of *C. difficile* strains.

Conclusion

Peripartum women with CDI have higher odds of undergoing cesarean delivery compared to those without the infection. CDI did not affect neonatal outcomes; however, larger studies are needed to confirm these findings. Increased awareness of peripartum CDI is warranted among both clinicians and patients to prevent adverse outcomes.

Authors' Note

Previous presentations: Part of the results from this study were presented at American College of Gastroenterology annual scientific meeting, 5–10 October 2018, Philadelphia, USA and at Digestive Diseases Week 18–21 May 2019, San Diego, USA.

Declarations

Ethics approval and consent to participate

Approval from Mayo Clinic IRB was obtained prior to conducting the study (IRB number: 18-003246; approved 4/13/2018 at Rochester, MN, USA). Informed consent was not taken due to the retrospective nature of the study. The IRB approved waiver for the requirement to obtain informed consent.

Consent for publication

Not applicable.

Author contribution(s)

Srishti Saha: Conceptualization; Data curation; Formal analysis; Visualization; Writing – original draft; Writing – review & editing.

Ryan Pardi: Data curation; Writing – review & editing.

Regan N. Theiler: Data curation; Methodology; Visualization; Writing – review & editing.

Darrell S. Pardi: Methodology; Resources; Writing – review & editing.

Sahil Khanna: Conceptualization; Methodology; Project administration; Resources; Software; Supervision; Visualization; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

By request to corresponding author.

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Supplemental material

Supplemental material for this article is available online.

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