



Contents lists available at ScienceDirect

# European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: [www.elsevier.com/locate/ejogrb](http://www.elsevier.com/locate/ejogrb)

Full length article

## Peritoneal adhesions are an independent risk factor for peri- and post-partum infectious morbidity

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## ARTICLE INFO

## Article history:

Received 12 June 2019

Received in revised form 2 August 2019

Accepted 5 August 2019

Available online xxx

## Keywords:

Puerperal infection

Repeat cesarean delivery

Surgical adhesion

## ABSTRACT

**Objective:** To investigate whether the presence of peritoneal adhesions during a second cesarean delivery resulting from the first cesarean delivery, are associated with peri- and post-partum infectious morbidity.

**Study Design:** A retrospective cohort study was undertaken, comparing maternal peri- and immediate post-partum infectious morbidity during the second cesarean delivery, between women with and without adhesions resulting from the first cesarean delivery. All women over 18 years old at their second cesarean delivery, with a singleton pregnancy between the years 1988–2016 were included in the analysis. Patients with previously diagnosed adhesions during the first cesarean delivery, a history of other abdominal or pelvic surgery, pelvic infection or pelvic inflammatory disease, endometriosis, uterine Mullerian anomalies, and births of newborns with known chromosomal or structural abnormalities were excluded from the analysis, resulting in a study population of 7925 women. Infectious morbidity was defined as a composite of chorioamnionitis, post-partum fever, urinary tract infection and surgical wound infection or disruption. In order to identify factors that are independently associated with infectious morbidity, multivariate logistic regression analyses were constructed to control for potential confounders.

**Results:** During the study period, 32.6% (n = 2581) women were diagnosed with adhesions at the second cesarean delivery. Second cesarean deliveries complicated with adhesions were characterized by higher rates of peri- and post-partum maternal infectious morbidity (6.5% vs. 9%, p < 0.001). Our study population comprises two ethnic groups- Jewish (54.3%) and Bedouin Arabs (45.7%). We have tested interactions with adhesions of all predictor variables in the model. Since we found a strong interaction between adhesions and ethnicity, stratified data are presented. Infectious morbidity was significantly associated with the presence of peritoneal adhesions only among Jewish women (adjusted OR 2.09, PV < 0.001, 95% CI 1.56–2.80), adjusting for potential confounding variables and significant interactions.

**Conclusion:** Cesarean delivery complicated with adhesions attributable to a previous cesarean delivery, increase the risk for peri- and immediate post-partum infectious morbidity among Jewish women.

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## Introduction

Adhesions are an abnormal fibrous connection between two anatomically different surfaces [1]. Peritoneal adhesion development can be stimulated by peritoneal irritation following surgical trauma, infection, inflammation, endometriosis and radiation. The majority of adhesions result from surgical interventions, and they may develop between the omentum, bowel, abdominal wall, intra-abdominal organs, and female pelvic organs [2–4].

The underlying pathophysiology results from increased extracellular matrix production, diminished matrix degradation, and decreased fibrinolytic activity that begins during the surgery and progresses rapidly thereafter [5].

Physiological changes during normal pregnancy promote adhesion formation. Adhesions were reported in 24%–46% of women at their second caesarean delivery (CD), and the incidence increases significantly after each subsequent CD [6,7].

While adhesion formation has little clinical effect on most patients, some patients may experience serious clinical consequences with a great impact on their health and quality of life [8]. The most severe complication is mechanical small bowel obstruction [8]. Pelvic adhesions are also associated with

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secondary infertility [9,10], increased risk for ectopic pregnancy [11], and chronic pelvic pain [12]. In patients undergoing repeated surgery, the presence of adhesions is associated with a higher risk of morbidity and mortality, technical difficulties and surgical complications that may include: inability to perform laparoscopic surgery and conversion to laparotomy, and damage to organs such as small bowel, bladder or the ureters [13,14].

Puerperal infection remains a significant cause for maternal morbidity and mortality. Approximately 10% of pregnancy related mortality in the US result from puerperal infection. CD is the single most important risk factor for puerperal infection, with an estimated 5 -to 20-fold increased incidence, resulting in major financial burden [15]. Multiple risk factors for post CD infections have been identified. Risk factors that may be modifiable include maternal obesity, tobacco use, hypertensive disorders of pregnancy, poorly controlled gestational diabetes, operating time, and surgeon experience. Non-modifiable risk factors include unscheduled CDs, previous CD, presence of active labor or rupture of membranes [16,17].

Most of the studies regarding maternal infectious morbidity after CD discuss the consequence of repeat CD, without specifically referring to the presence of adhesions. In these studies, the risk for infectious morbidity appeared to be controversial. Some studies demonstrated that repeat CD increased maternal complications, while others did not [18].

The purpose of this study was to investigate whether the presence of adhesions during the second CD resulting from the first CD, is associated with peri- and post-partum infectious morbidity.

## Materials and methods

A retrospective cohort study was conducted to compare peri- and post-partum maternal infectious morbidity following the second CD, between women with and without adhesions resulting from the first CD.

Study population (Fig. 1): Our cohort study included 9767 women over the age of 18 years at their second CD, who had at least two CDs. Women were included if they delivered a singleton in their second CD, at the Soroka University Medical Center (SUMC), Israel, between the years 1988–2016.

Our study was composed of both Jewish (54.3%) and Bedouin Arab (45.7%) patients.

To limit the study group to women with adhesions attributed to a previous CD, we excluded women with adhesions already diagnosed during the first CD (n = 341), history of other abdominal or pelvic surgery (n = 116), history of pelvic infection or pelvic inflammatory disease (n = 16), or history of endometriosis (n = 42). In addition, women with uterine Mullerian anomalies (n = 467) and births resulting in a newborn with known chromosomal or structural abnormalities (n = 1087) were excluded. Finally, 1842 women who had one or more of the above mentioned conditions were excluded, leaving 7925 women for analysis.

## Data

The primary exposure variable was the presence of adhesions during the second CD, resulting from the first CD. These data were collected

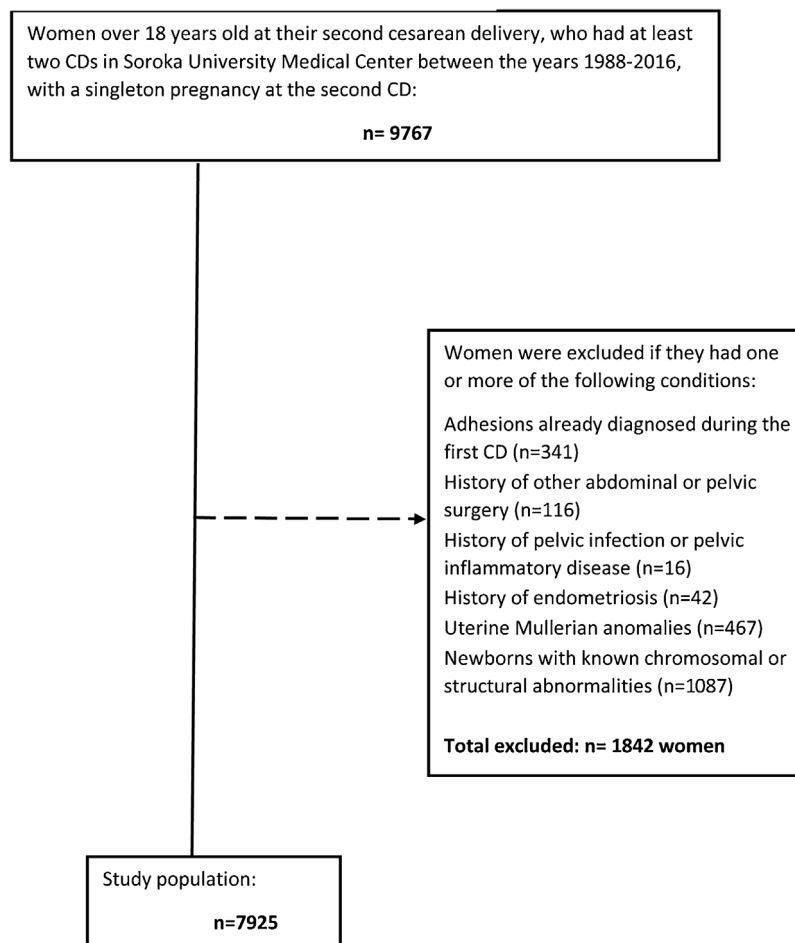


Fig. 1. Study population flow chart.

**Table 1**  
Baseline characteristics at the second cesarean delivery of women with and without adhesions.

Characteristics	Adhesions n = 2,581	No adhesions n = 5,344	P
Maternal age (years ± SD)	30.8 ± 5.5	31.1 ± 5.4	0.035
Ethnicity			
Jewish (%)	49.1	56.9	<0.001
Bedouin (%)	50.9	43.1	
Gravidity (median, inter quartile range)	3 (2-5)	3 (2-6)	0.008
Parity (median, inter quartile range)	2 (2-5)	3 (2-5)	0.040
Time interval (median months since the 1st CD, inter quartile range)	35 (22-60)	38 (23-66)	<0.001
Number of pregnancies between the two CDs (median, inter quartile range)	0.0 (0-1)	0.0 (0-1)	<0.001
Number of births between the two CDs (median, inter quartile range)	0.0 (0-0)	0.0 (0-0)	0.003
Recurrent pregnancy losses <sup>a</sup> (%)	5.9	7.2	0.028
Fertility treatments (%)	3.8	3.6	0.743
Smoking (%)	2.9	3.0	0.720
DM (%)	4.0	3.9	0.864
Obesity (%)	2.2	1.3	0.004
Chronic HTN (%)	3.4	3.3	0.961

P P-value, SD standard deviation, CD cesarean delivery, DM Diabetes mellitus, Chronic HTN Chronic hypertension.

<sup>a</sup> Defined as 3 or more pregnancy losses.

from the surgical reports. These adhesions were considered as attributable to the first CD, since they were not present in the first CD and since women with other potential causes of adhesion occurring after the first CD were excluded. The primary composite outcome of peripartum and immediate post-partum infectious morbidity was defined as infectious morbidity that occurred during labor and up to the time of discharge from the hospital following delivery. Infectious morbidity included: chorioamnionitis (ICD-9 code 658.41), post-partum fever (ICD-9 codes 672.02, 670.02), urinary tract infection (ICD-9 code 646.62), and surgical wound infection or disruption (ICD-9 codes 674.1, 674.10, 674.11, 674.12, 674.32).

The following variables in the second CD were examined as control variables: Baseline characteristics, including maternal age, ethnicity, gravidity, parity, time interval since the 1<sup>st</sup> CD, number of pregnancies and births between the CDs, recurrent pregnancy losses, fertility treatments, smoking, pregestational diabetes, obesity and chronic hypertension. Obstetric history including: gestational age, preterm delivery below 34 and 37 weeks, lack of prenatal care (LOPC), hypertensive disorders of pregnancy, intrauterine growth restriction (IUGR), gestational diabetes, and premature rupture of membranes (PROM) or preterm premature rupture of membranes (PPROM). We also examined diagnoses that were given during the CD: non-reassuring fetal heart rate (NRFHR), non-progressive labor- first and second stage, failed vacuum extraction, placental abruption, cord prolapse, cephalopelvic disproportion, placenta previa, placenta accreta, vasa previa, malpresentation, macrosomia, and maternal request. Finally, we examined perinatal outcomes, including type of anesthesia, type of uterine incision, birthweight, and perinatal mortality.

Data were collected from hospital's computerized obstetrics and gynecology database. The database consists of information recorded immediately after delivery.

**Table 2**  
Peri- and post-partum Infectious morbidity at the second cesarean delivery of women with and without adhesions.

Characteristics	Adhesions n = 2,581	No adhesions n = 5,344	P
Composite infectious morbidity (%)	9.0	6.5	<0.001
Chorioamnionitis (%)	1.8	1.8	0.968
Post-partum fever (%)	2.6	1.8	0.014
Urinary tract infection (%)	0.4	0.3	0.447
Surgical wound infection or disruption (%)	4.6	3.0	<0.001

P P-value.

Composite infectious morbidity includes at least one of the following diagnosis: chorioamnionitis, post-partum fever, urinary tract infection and surgical wound infection or disruption.

Women may have been included in more than one category.

Statistical analysis was performed using the SPSS package 23 ed. Unadjusted rates and means were compared using Pearson  $\chi^2$ , Student's unpaired *t*-test, and Mann-Whitney rank sum U-test, as appropriate for categorical, normally distributed continuous variables, and continuous variables without normal distribution, respectively.

After assessing the presence of collinearity and identification of potential confounders and interactions, variables found to be significant in the univariate analysis, in addition to variables with clinical significance regardless of statistical significance at the univariate analysis, were included in the multivariable logistic regression model. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were computed. A P-value of < 0.05 was considered statistically significant.

The study was approved by the SUMC institutional review board (# SOR- 0146-17).

## Results

Of the study population, 32.6% (n = 2581) were diagnosed with adhesions during the second CD resulting from the first CD. Peri- and immediate post-partum infectious morbidity was diagnosed in 580 (7.3%) of women.

Table 1 compares baseline characteristics at the second CD of women with and without a diagnosis of adhesions. Mean maternal age at the second CD was significantly lower among women with adhesions, as was the median gravidity, parity, time interval, and both number of pregnancies and the number of births between the two CDs. Second CDs complicated with adhesions, compared to those without adhesions, were also characterized by higher proportions of Bedouin women, maternal obesity, and lower rates of recurrent pregnancy losses.

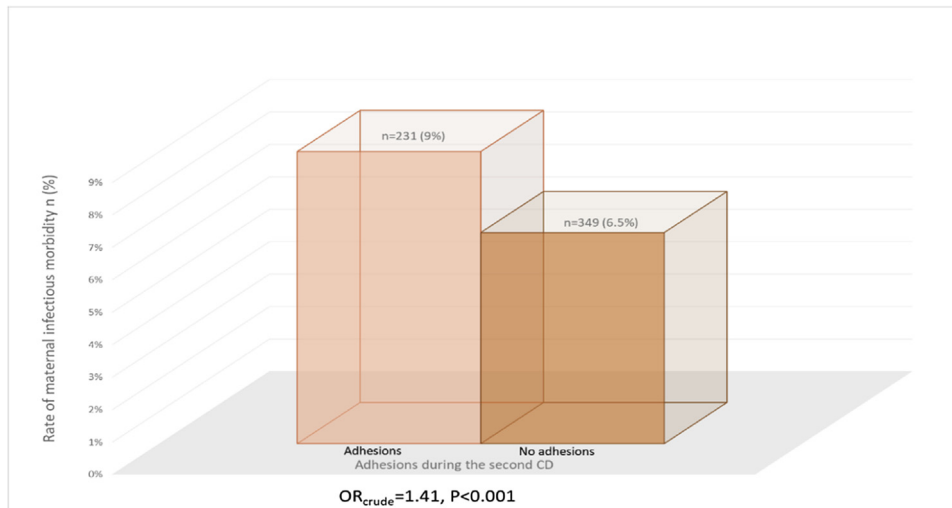


Fig. 2. Rate of maternal infectious morbidity in women with and without adhesions.

Table 2 compares peri- and post-partum Infectious morbidity at the second CD, among women with and without adhesions. Second CDs complicated with adhesions were characterized by higher rates of peri- and post-partum maternal infectious morbidity as a composite (Fig. 2), and specifically significantly higher rates of post-partum fever and surgical wound infection or disruption.

Table 3 compares obstetrical characteristics and perinatal outcomes at the second CD, among women with and without adhesions. Mean gestational age and mean birthweights were

significantly higher among women with adhesions. Second CDs complicated with adhesions were characterized with higher rates of PROMPPROM, NRFHR and Non-progressive labor- 2<sup>nd</sup> stage, and lower rates of preterm delivery rates (both below 37 weeks and 34 weeks), IUGR, placental abruption and malpresentation.

To assess the independent effects of adhesions we performed a multivariate logistic regression analysis controlling for variables from the second CD found to be significant in the univariate analysis, in addition to variables with clinical significance

Table 3

Obstetrical characteristics and perinatal outcomes at the second CD of women with and without adhesions.

Characteristics	Adhesions n = 2,581	No adhesions n = 5,344	P
Mean gestational age at delivery (week ±SD)	38.7±2.2	38.5±2.3	0.008
Preterm<37 weeks (%)	9.3	10.7	0.048
Preterm<34 weeks (%)	2.6	3.6	0.022
LOPC (%)	5.0	4.7	0.507
Hypertensive disorders of pregnancy <sup>a</sup> (%)	6.5	6.6	0.869
IUGR (%)	2.8	4.0	0.006
GDM (%)	7.2	7.1	0.828
PROM or PPROM (%)	11.4	9.8	0.024
CD indication			
NRFHR (%)	14.1	10.7	<0.001
Non-progressive labor- 1 <sup>st</sup> stage (%)	15.6	14.3	0.126
Non-progressive labor- 2 <sup>nd</sup> stage (%)	4.0	3.0	0.023
Failed vacuum extraction (%)	0.6	0.4	0.431
Placental abruption (%)	1.6	2.6	0.006
Cord prolapse (%)	1.5	1.1	0.120
CPD (%)	1.0	1.4	0.092
Placenta previa (%)	1.8	2.1	0.323
Placenta accreta Vasa previa (%)	0.4	0.4	0.925
Malpresentation <sup>b</sup> (%)	14.8	17.1	0.009
Macrosomia (%)	1.5	1.3	0.388
Maternal request (%)	14.2	14.4	0.803
Type of anesthesia			
General (%)	78.0	76.1	0.061
Regional (%)	22.0	23.9	
Type of uterine incision			
Low cervical (%)	98.6	99.0	0.13
Classical or T-shaped (%)	1.4	1.0	
Birthweight (grams, mean ± SD)	3249.8±605.9	3,218.1±644.3	0.032
Birthweight			
<2500 grams (% LBW)	9.7	10.7	0.305
2500–4000 grams (%)	81.4	80.0	
<4000 grams (%)	8.9	9.3	
Perinatal mortality (%)	0.8	1.2	0.092

P P-value, SD standard deviation, LOPC lack of prenatal care, IUGR Intrauterine growth restriction, GDM gestational diabetes mellitus, PROM Premature rupture of membranes, PPROM preterm premature rupture of membranes, NRFHR non- reassuring fetal heart rate, CPD Cephalopelvic disproportion, LBW low birth weight.

<sup>a</sup> Defined as composite of pregnancy induced hypertension, pre eclamptic toxemia and eclampsia.

<sup>b</sup> Defined as any presentation other than vertex.

**Table 4**

Results of a multivariable logistic regression analysis with infectious morbidity as the outcome variable, analyzed by ethnicity.

Population	Characteristics of the 2 <sup>nd</sup> CD	Adjusted OR	CI 95%	P- value
Jewish	<b>Adhesions</b>	<b>2.09</b>	<b>1.56-2.80</b>	<b>&lt;0.001</b>
	Parity	1.71	1.13-2.57	0.011
	Gestational age (weeks)	0.60	0.45-0.82	0.001
	PROMPPROM	3.06	2.03-4.61	<0.001
	Non- progressive labor first stage	1.83	1.28-2.62	0.001
	Maternal request	0.58	0.37-0.90	0.016
Bedouin Arab	<b>Adhesions</b>	<b>1.18</b>	<b>0.91-1.54</b>	<b>0.216</b>
	Parity	1.34	1.01-1.79	0.042
	Gestational age (weeks)	0.67	0.51-0.89	0.005
	Time interval since the 1 <sup>st</sup> CD (months)	0.77	0.60-0.99	0.043
	Type of uterine incision (Low cervical classical or T-shaped)	2.64	1.28-5.44	0.008
	Perinatal mortality	2.04	1.01-4.11	0.046
	PROMPPROM)	2.15	1.46-3.18	<0.001
	Non- progressive labor first stage	1.42	1.07-1.90	0.017
	Non- progressive labor second stage	1.70	1.02-2.83	0.042
	Placenta previa	2.02	1.06-3.88	0.034

OR odds ratio, CI confidence interval, P P-value, PROM Premature rupture of membranes, PPROM preterm premature rupture of membranes.

Except for adhesion, variables shown in the table are those with P values under 0.05.

The model in Jewish population was also adjusted for the following variables: maternal age, time interval since the 1<sup>st</sup> CD, birthweight, type of uterine incision, type of anesthesia, perinatal mortality, NRFHR, non-progressive labor second stage, placental abruption, placenta previa and interaction variable between adhesions and PROMPPROM.

The model in Bedouin Arab population was also adjusted for the following variables: maternal age, birthweight, type of anesthesia, non-reassuring fetal heart rate, placental abruption, maternal request and interaction variable between adhesions and PROMPPROM.

regardless of statistical significance at the univariate analysis. The following potential confounding variables were included in the model: ethnicity, maternal age, parity, gestational age, time interval since the 1<sup>st</sup> CD, birthweight, type of uterine incision, type of anesthesia, perinatal mortality, NRFHR, non-progressive labor first & second stage, placental abruption, placenta previa, maternal request. Adhesions were found to be independently associated with peri- and immediate post-partum infectious morbidity (adjusted OR 1.39,  $P < 0.001$ , CI 1.16–1.66). We have tested interactions with adhesions of all predictor variables in the model, and found a strong interaction between adhesions and ethnicity. We therefore conducted multivariate analyses separately for each ethnic group, adjusting for the same potential confounding variables and significant interactions. In this analysis a significant association with adhesions was found only among Jewish women (adjusted OR 2.09,  $P < 0.001$ , CI 1.56–2.80), but not among Bedouin Arab women (Table 4).

We performed similar multivariate analyses for each component of the composite outcome, separately in each ethnic group. Chorioamnionitis (adjusted OR 2.29,  $P = 0.019$ , CI 1.15–4.56), post-partum fever (adjusted OR 2.01,  $P = 0.014$ , CI 1.15–3.50), and surgical wound infection or disruption (adjusted OR 2.03,  $P < 0.001$ , CI 1.39–2.97) were found to be significantly associated with the presence of peritoneal adhesions in the second CD only among Jewish women (table S1).

## Comment

In the current study we aimed to investigate whether the presence of peritoneal adhesions during a second CD resulting from the first CD, are associated with peri- and post-partum infectious morbidity. We were able to demonstrate an independent association between adhesions and maternal infectious morbidity. This association was found with the predefined composite outcome, as well as separately with post-partum fever and surgical wound infection.

Adhesions typically result from surgical interventions. The underlying pathophysiology is attributed to increased extracellular matrix production, diminished matrix degradation, and decreased

fibrinolytic activity that begins during the surgery and progresses rapidly thereafter [5]. Surgical interventions cause tissue damage that result in bleeding and lymphatic fluid leakage. Consequently, a complex inflammatory cascade augments fibrin clot formation that cover the injured tissue [1,19,20]. When the fibrinolytic activity is diminished, the fibrinous mass persists, and the fibroblast ingrowth process will progress and form connections between the tissue surfaces. Vascularization and innervation of the connections form the adhesions may follow [1,19,21].

Physiological changes during normal pregnancy promote adhesion formation. There is a marked increase in the procoagulant activity, and additionally a significant reduction in physiological anticoagulants [22]. However, it should be noted that intraperitoneal adhesions following CD are less prevalent compared to adhesions following other abdominal surgeries [6].

Most of the studies dealing with maternal infectious morbidity after CD did not specifically refer to the presence of peritoneal adhesions. Our findings are in accordance with a study that found that women who underwent adhesiolysis during CD were more likely to have complications including infections (OR 1.54,  $p = 0.003$ ) and wound complications (OR 1.91,  $p < 0.001$ ) [23]. It should be noted that the study was funded by Ethicon, Inc., a company that manufactures adhesion barrier agents.

Several interventions have been shown in the literature as effective in reducing the risk for post CD infectious complications. These interventions include administering preoperative antibiotics within 60 min of CD, chlorohexidine-alcohol rather than povidone-iodine based solutions for skin antisepsis, suture closure of the subcutaneous layer in women with above 2 cm subcutaneous tissue, and subcuticular skin closure rather than staples [15]. In our institution post CD infection prevention strategies are generally in accordance with those recommendations.

Patients in SUMC are mainly composed of two ethnic groups: Jewish and Bedouin Arabs. Both groups, as all Israeli citizens, are covered by National Health Insurance, served by the same prenatal services and give birth in the same regional hospital. In our study peri- and post-partum infectious morbidity was more common among Bedouin Arab patients. Interestingly, after taking into consideration the strong interaction between adhesions and ethnicity, we have



shown that the effect of adhesions is significantly associated with peri- and post-partum infectious morbidity only for the Jewish population. The Bedouin Arab minority is a Muslim community, characterized by lower socio-economic status, higher rates of consanguineous marriage, higher gravidity and parity, shorter interval between births, pregnancies at an early age, and reduced use of prenatal care services [24]. Previous studies on our population demonstrated significant associations between Bedouin Arab ethnicity and adverse pregnancy outcomes [25]. It is possible that due to the many risk factors for poor pregnancy outcomes and infectious morbidity among Bedouin Arab patients, the effect of adhesions on infectious morbidity is less substantial, and therefore was not statistically significant.

Our study offers several strengths. The main strength is the large sample size, which allowed us to assess the implications of adhesions more precisely, controlling for potential confounders. In addition, the fact that our hospital is the sole tertiary hospital in southern Israel, serving the entire population of the region, ensures that our study is based on a non-selective population sample.

The limitations of our study are the inherent faults of retrospective cohort studies. The medical records may demonstrate under-reporting of the true incidence of the variables that have been studied, however it should be noted that the information in the database is recorded by an obstetrician immediately following the delivery, and is routinely checked by skilled medical secretaries for inaccuracies. In addition, our database lacks detailed information about further potential confounders such as the location and severity of the adhesions, use of antiadhesive agents, level of experience of the surgeons performing the CD, and the operative time. Another limitation is the lack of information about the classification of the CD as emergent or elective surgery. Emergent CDs are a known risk factor for post-partum infectious morbidity [15]. To deal with this fault, we adjusted the multivariate model for the indications for the CD. Finally, our study refers to the possible impact of adhesions on infectious morbidity only during the immediate hospitalization period and does not reflect the infectious morbidity encountered after discharge from the hospital.

In conclusion, CD complicated with adhesions attributable to previous CD, elevates the risk for peri- and immediate post-partum infections. Using established strategies to prevent infectious morbidity (such as preoperative antibiotics administration, chlorohexidine-alcohol use for skin antisepsis, suture closure of the subcutaneous layer and subcuticular skin closure) should be encouraged especially in women with adhesions. Interventions aimed at reducing adhesions during the primary CD (such as use of adhesion barriers) should be farther investigated and evidence base recommendations made.

## Funding

This study was not funded.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ejogrb.2019.08.001>.

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