Maternal Health, Neonatology and Perinatology

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Impact of COVID-19 in pregnancy on maternal and perinatal outcomes during the Delta variant period: a comparison of the Delta and pre-delta time periods, 2020–2021

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Abstract

Background To describe the impact on maternal and perinatal outcomes of the Delta variant of COVID-19 compared to the pre-Delta period in pregnant women with COVID-19 infections in one large public, non-profit hospital system.

Methods We conducted a retrospective chart review of identified COVID-19 diagnosed pregnant women with the outcome of pregnancy (livebirth or stillbirths). We assessed maternal and perinatal outcomes between the pre-delta and Delta variant time periods.

Results A study cohort of 173 mother-baby dyads was identified from January 2020 to November 2021. Maternal outcomes showed a higher rate of cesarean section (33.8%,49%; $p=0.047$), with a higher frequency for worsening maternal condition due to COVID-19 (2.8%, 13.7%; $p=0.016$) and association with non-reassuring fetal heart tones as indications for cesarean Sect. (53.8%, 95%; $p=0.008$) during the Delta time period. There were more preterm births (16.9%, 32.4%; $p=0.023$) even when excluding stillbirths (16.9%,30%; $p=0.05$). Cesarean section due to "worsening maternal condition" was an independent risk factors for early delivery ($\beta=2.66$, 93.32–62.02, $p<0.001$). The neonates had a longer mean (7.1 days, 9.9 days; $p<0.001$) and median (2 days, 3 days; $p<0.001$) length of stay during the Delta period. There was no difference in Apgar scores, NICU admissions or need for respiratory support between time periods.

Conclusion In a public, non-profit health system, from January 2020 to November of 2021, mothers with a diagnosis of COVID-19 during pregnancy, there were more preterm deliveries during the Delta time period, as well as longer length of stay for liveborn babies.

Keywords COVID-19, SARS-CoV-2, Delta variant, Pregnancy, Pregnant women, Maternal outcomes, Perinatal outcomes, Stillbirths, Preterm birth

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Background

Although infections with the SARS-CoV-2 (COVID-19) virus have moved into an endemic phase, our understanding of the impact of the COVID-19 pandemic continues to evolve. The literature describes the impact of COVID-19 variants on perinatal outcomes since the first reported national cases in the early months of 2020, through the rise of cases in the fall and winter months of 2020 [1], through the emergence of the more transmissible Delta variant [2, 3] in the early summer of 2021 and the subsequent emergence of the Omicron variant in late 2021 [4, 5]. Several studies have reported an increased risk of maternal morbidities, preterm births and stillbirths, and variable neonatal outcomes during this phase [6–12]. Additional studies have reported an increase in these adverse outcomes during the emergence of the Delta variant 10, 15–17. In the southwest Florida community, we experienced increased COVID-19 related pregnancy admissions with delivery beginning in July of 2021, which mirrored our overall nonpregnant persons hospital admission trends (Figs. 1 and 2). Our cohort is derived from a single community-based health care system, with over 7,000 annual livebirths, with facilities located in Fort Myers and Cape Coral, Florida. It is one of 11 regional perinatal intensive care center (RPICC) programs in the state of Florida, with level III maternal and neonatal care services located at the Fort Myers facility, and level II maternal care at the Cape Coral facility.

The study comparatively describes two time periods and the impact of COVID-19 infection during pregnancy on hospitalized pregnant women, delivery outcomes and neonatal impact, in a community setting.

Methods

Study design, data source, study population

We conducted a retrospective chart review of pregnant women diagnosed with COVID-19 between January 2020 and November 2021 within Lee Health System. We established time periods using available epidemiologic data. We did not have the local ability to utilize rapid antigen detection or whole genome or S-gene sequencing testing for the Delta variant. Following the onset of the pandemic in early 2020, there was a second wave, a surge in COVID-19 cases beginning in early July, 2021. [1] Overall trended cases in Florida mark the first wave with peaks in July 2020 and Dec 2020-Jan 2021, followed by a more accentuated, second wave beginning in July 2021. [2] This is reflected in total cases, hospital admissions, and new deaths [13, 14]. The study timeframe was defined as follows. The presumed emergence of the Delta variant or second wave timeframe included all identified PCR-based COVID-19-diagnosed mothers with a hospitalization outcome to pregnancy – beginning July 1, 2021, and ending November 30, 2021. The comparison group were all identified COVID-19-diagnosed mothers with a hospitalization outcome to pregnancy - January 1, 2020, to June 30, 2021 (although our first eligible mother: baby dyad was identified in April, 2021). Our cohort is derived from HealthPark Medical Center in Fort Myers (RPICC center) and Cape Coral Hospital, Cape Coral (level II maternity service), Florida. Both of the facilities are located in Lee county with about a 7% catchment rate for deliveries from surrounding counties. Neonatal ICU care is located at Golisano Children's Hospital of Southwest Florida, which is adjacent to HealthPark Medical Center.

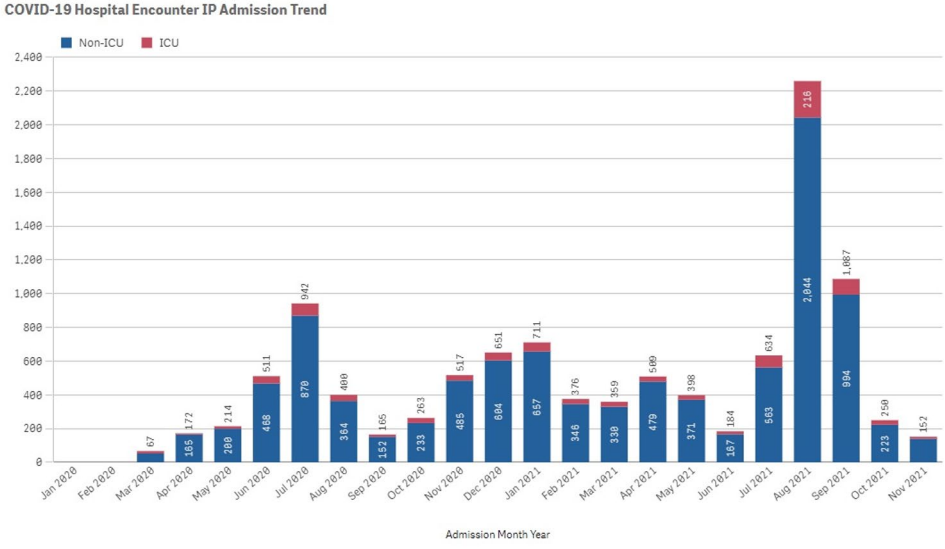

Fig. 1 Lee health COVID-19 daily in-patient monthly admissions: second wave beginning July, 2021 through November, 2021

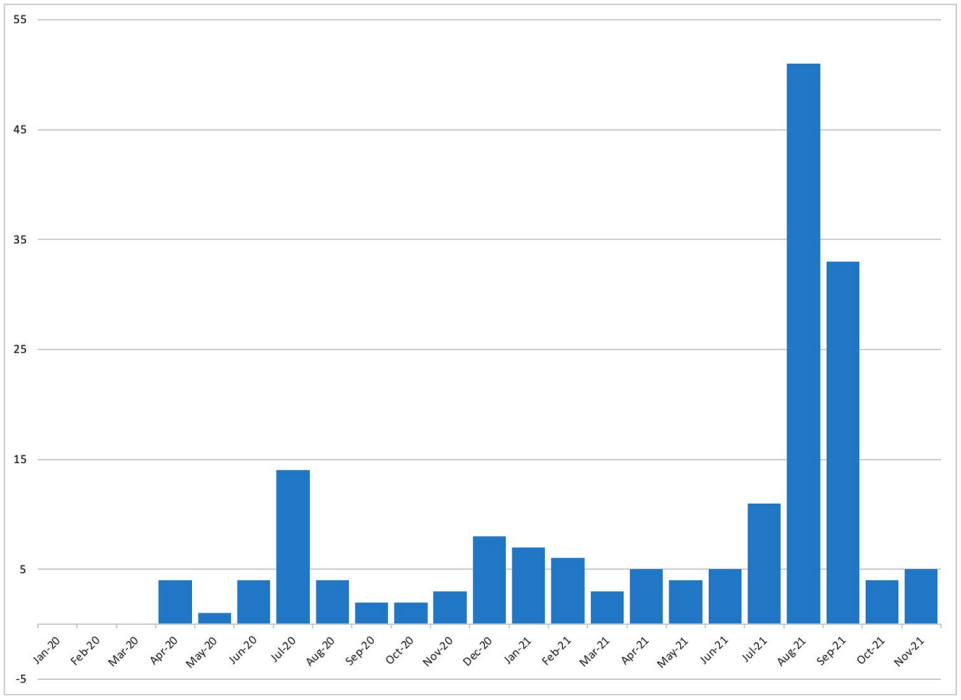

Fig. 2 COVID-19 Pregnancies with delivery by month: January 2020 to November 2021

We identified eligible patients by utilizing the following search strategies from January 1, 2020, to November 30, 2021. Eligible patients were identified using Cogito Slicer-Dicer (Epic Systems, Verona, WI) [18, 19], a data extraction tool provided by the healthcare system electronic medical records, to identify all births and crosslinked to their hospitalized obstetrical encounter diagnosis of COVID-19 (ICD-10 coding). Additionally, all obstetrical, newborn, and NICU admission logs which listed any admitted mother with a diagnosis of COVID-19 were extracted. Collection of total maternal COVID-19 diagnosed admissions and the maternal, fetal and neonatal outcomes were completed by assessing the EPIC electronic health records database using Clarity (Oracle, Austin, TX), with queries using SQL Server (Microsoft, Redmond, WA). This cohort was verified for accuracy, and characteristics tabulated by direct chart review.

Study population

We identified mother and baby dyads and considered them eligible if there was a hospitalized outcome to the pregnancy (live birth or stillbirth, greater than 20 weeks), and a diagnosis of COVID-19 during the pregnancy, at or during admission for delivery, or post-partum while the baby was hospitalized, up to 10 days following delivery for hospitalized newborns.

We initially identified 195 mother: baby dyads. Among them 192 original mothers with a diagnosis of COVID-19 during pregnancy, and 195 babies. The earliest patient was born on March 18, 2020 and the last baby was on November 24, 2021. From this group, 19 mothers and 19 babies were excluded. Reasons for exclusion: 16 mothers did not meet criteria for a diagnosis of COVID-19 (insufficient history and/or lack of confirmatory testing) during the pregnancy (7 pre-Delta and 9 Delta); 1 mother had COVID-19, but prior to pregnancy; 1 mother developed COVID-19 more than 10 days after birth; and 1 was a duplicate patient. The study included 173 pregnant women and 176 delivery outcomes. Of these, there were 3 twin pregnancies (1 born in pre-Delta time period: diamnionic, dichorionic twin at 33+2 weeks, and 2 Delta twins: discordant, diamnionic, dichorionic at 33+4 weeks and diamnionic, monochorionic at 37 weeks), and 5 fetal deaths (1 pre-Delta: 29 weeks, and 4 Delta: 22 weeks, 22+6 weeks, 26+1 weeks, 24+4 weeks and 29 weeks). There were 173 mothers and 176 delivery outcomes reviewed from April 2020 to November 2021 (Fig. 2).

Definition of variables

The diagnosis of COVID-19 was defined as a positive confirmatory test (SARS Coronavirus-2 RNA Qualitiative; ID NOW SARS CoV-2 assay; Abbott Diagnostics, Scarborough, Inc), a patient history of COVID-19 diagnosis during pregnancy and maternal symptoms consistent with a diagnosis of COVID-19, or a patient admitted as a Person of Interest (PUI) due to symptoms suspicious of COVID-19. Variables were confirmed by chart review and based upon assessment by one of the principle investigator's (CM), a patient with symptoms (febrile > 100.3°

F, cough, dyspnea, fatigue) consistent with COVID-19 infection were included in the study cohort.

Outcome variables

Maternal characteristics such as age, parity ethnicity, race, Body Mass Index (BMI), timing of COVID-19 diagnosis during pregnancy, medication use, oxygen requirement, preterm labor, perinatal diagnoses, rupture of membrane (ROM), type of delivery, routine of delivery, indications for induction of labor (IOL) due to maternal and/or perinatal factors, cesarean section (c-section) due to maternal and/or perinatal factors (worsening maternal condition), and postpartum complications. C-section secondary to worsening maternal condition specifically due to COVID 19 was defined when listed as the predelivery indication, secondary to need for increased oxygen requirement and/or need for higher level of care/transfer. Maternal outcomes were measured as preterm delivery, required hospitalization due to COVID-19, intensive care unit (ICU) admission, transfers of care to higher level of care to outside facilities for extracorporeal membrane oxygenation (ECMO) requirement or other critical care needs. There were no maternal deaths recorded.

Neonatal baseline characteristics such as infant disposition, multiplicity, gestational age (GA), birth weight (BW), with small for gestational age (SGA) defined as less than 10% for weight, gender, ethnicity, race, APGAR scores, growth status, delivery room (DR) resuscitation status, neonatal COVID-19 testing status, need of respiratory support, and length of stay (LOS). The outcome of delivery was determined as either a live birth or a stillbirth. Stillbirth was defined as any fetal death that was greater than or equal to 20 weeks gestation, and the stillbirth rate was calculated as stillbirth divided by total births (live births + stillbirths) multiplied by 1000.

Statistical analysis

Using SPSS version 26.0 (IBM Corp, Armonk, NY), median with interquartile range (IQR) were reported for continuous variables, and proportions were reported for categorical variables. In bivariate analysis, the Chi-square or Fisher's exact test, as appropriate, compares proportions, and the Mann-Whitney *U* test compares continuous variables between pre-Delta and Delta groups. In bivariate analysis, those that were significant were included in the multivariable regression analysis. Statistical significance is defined as a $p <= 0.05$.

This study received IRC approval by the Lee Health Institutional Review Committee.

Results

Maternal baseline characteristics and outcomes are summarized in Tables 1 and 2. In the Delta group, more mothers were diagnosed with COVID-19 between 1 and 14 days prior to delivery (33.8%,57.8%; $p=0.002$). The pre-Delta group had more mothers diagnosed with COVID-19 further away from delivery, 15–30 days prior to delivery (19.7%,7.8%; $p=0.021$). During the pre-Delta time period, more mothers were being documented to be symptomatic (88.1%, 75%; $p=0.039$). During the Delta time period, patients received more antiviral (remdesivir) (5.6%, 23.5%; $p=0.001$)and more anticoagulant (enoxaparin or heparin) treatment, (4.2%, 13.7%; $p=0.042$).

The proportion of artificial rupture of membrane (AROM) was higher during the Delta time period compared to the pre-Delta time period (28.2%, 59.8%; $p<0.001$). There was a higher rate of c-section in the Delta group (33.8%, 49%; $p=0.047$). Looking at the listed maternal risk factors for c-section for the Delta group, there was a suggestion of greater association with c-sections due to "worsening maternal condition" (11.3%,22.5%; $p=0.057$) and noted to be significantly associated with "worsening maternal condition due to COVID-19" (2.8%, 13.7%; $p=0.016$) (Table 1). The Delta time period had more c-sections due to non-reassuring fetal heart tones (53.8%, 95%; $p=0.008$). Two patients were transferred to outside facilities, one was transferred to another facility requiring ECMO, following her c-section during the pre-Delta time period. She returned back to our facility five days later and was discharged home on post-operative day 11. The other patient delivered during the Delta time period by c-section, suffered multiple pulmonary complications, was never successfully extubated, required tracheostomy and eventually was transferred (6.5 months from delivery) to a regional transplant center, awaiting lung transplant.

There were more preterm deliveries during the Delta time period (16.9%, 32.4%; $p=0.023$). A binary logistic regression analysis with preterm delivery as the dependent variable found c-section due to "worsening maternal condition" as the only independent risk factors for early delivery ($\beta=2.67$, 95% CI[3.33–62.03], $p<0.001$) (Table 3).

For COVID-19 pregnancies, there were a total of five stillbirths during the study period, one during the pre-Delta and four during the Delta time periods. All stillbirths were delivered preterm (22–29 weeks). The number of stillbirths between pre-Delta and Delta groups were not significantly different.

Neonatal outcomes are summarized in Table 4. Excluding stillbirths, compared to the pre-Delta group, there was a higher number of liveborn preterm births in the Delta group (16.9%,30%; $p=0.05$).

Table 1 COVID-19 pregnancy: maternal characteristics and perinatal outcomes: Jan 2020 - Nov 2021

Maternal characteristics & outcomes	Total study population *N* = 173	Pre-delta *n* = 71 (%)	Delta *n* = 102 (%)	*p*-value[a]
Age, median (IQR)	29 (25–33)	28 (24–33)	29 (27–33)	0.442
Parity, n, median (IQR) (*n* = 172)	1 (0–2)	1 (0–2)	1 (0–2)	0.292
Birth Facility				
Health Park- level III maternity care and NICU	130 (75.1)	53 (74.6)	77 (75.5)	0.9
Cape Coral- level II maternity care	43 (24.9)	18 (25.4)	25 (24.5)	
Ethnicity				
Hispanic	71 (41)	33 (46.5)	38 (37.3)	0.338
Non-Hispanic	101 (58.4)	38 (53.5)	63 (61.8)	
unknown	1 (0.6)	0 (0)	1 (1)	
Race				
Asian	2 (1.2)	1 (1.4)	1 (1)	0.772
Black	22 (12.7)	11 (15.5)	11 (10.8)	
White	142 (82.1)	57 (80.3)	85 (83.3)	
None of the above	5 (2.9)	2 (2.8)	3 (2.9)	
unknown	2 (1.2)	0 (0)	2 (2)	
Basal Metabolic Index (BMI)				
Basal Metabolic Index (BMI), median (IQR)	31.1 (26.7–36.5)	31.2 (25.8–37.3)	30.95 (27.3–36.4)	0.907
BMI Group				
Underweight (< 18.6)	1/170 (0.6)	0/70 (0)	1/100 (1)	0.727
Normal (18.6–24.9)	28/170 (16.5)	14/70 (20)	14/100 (14)	
Overweight (25–29.9)	39/170 (22.9)	15/70 (21.4)	24/100 (24)	
Obese (> = 30)	102/170 (60)	41/70 (58.6)	61/100 (61)	
Obesity Group				
Obese (BMI 30.0–34.9)	49/102 (48.1)	19/41 (46.3)	30/61 (49.2)	0.368
Obese (BMI 35.0–39.9)	30/102 (29.4)	10/41 (24.4)	20/61 (32.8)	
Obese (BMI > = 40.0)	23/102 (22.5)	12/41 (29.3)	11/61 (18)	
Timing of COVID-19 Diagnosis				
Diagnosed within 10 days after delivery	4 (2.3)	2 (2.8)	2 (2)	1
Diagnosed on the day of delivery	26 (15)	14 (19.7)	12 (11.8)	0.15
Diagnosed within 1–14 days prior to delivery	83 (48)	24 (33.8)	59 (57.8)	**0.002**
Diagnosed within 15–30 days prior to delivery	22 (12.7)	14 (19.7)	8 (7.8)	**0.021**
Diagnosed > 30 days prior to delivery	38 (22)	17 (23.9)	21 (20.6)	0.6
Required hospitalization due to COVID-19 before delivery	31/135 (23)	7/50 (14)	24/85 (28.2)	**0.058**
Clinical Status of known COVID-19 infection at admission that included delivery				
Asymptomatic	32/ 163 (19.6)	8/67 (11.9)	24/96 (25)	**0.039**
Symptomatic	131/163 (80.4)	59/67 (88.1)	72/96 (75)	
Newborn Outcome				
Live Birth	171 (97.2)	71 (98.6)	100 (96.2)	0.65
Stillborn	5 (2.8)	1 (1.4)	4 (3.8)	
Perinatal diagnoses				
Third-trimester vaginal bleeding	6 (3.5)	2 (2.8)	4 (3.9)	1
Hypertensive Disorder of Pregnancy	29 (16.8)	14 (19.7)	15 (14.7)	0.385
Preterm – Labor	19 (11)	8 (11.3)	11 (10.8)	0.92
Other[b]	11 (6.4)	7 (9.9)	4 (3.9)	0.115
Type of Labor				
Spontaneous	131/167 (78.4)	50/65 (76.9)	81/102 (79.4)	0.703
Induced	36/167 (21.6)	15/65 (23.1)	21/102 (20.6)	
Induction of Labor Maternal primary Indication				
Post date (greater than 40 weeks 6 days)	4 (2.3)	1 (1.4)	3 (2.9)	0.645
Advance Maternal Age (age 35 and older)	3 (1.7)	3 (4.2)	0 (0)	0.067
Obesity (> 29.9)	6 (3.5)	5 (7)	1 (1)	**0.043**
Hypertensive Disorder of Pregnancy (preeclampsia/severe preeclampsia)	11 (6.4)	6 (8.5)	5 (4.9)	0.362

Table 1 (continued)

Maternal characteristics & outcomes	Total study population *N* = 173	Pre-delta *n* = 71 (%)	Delta *n* = 102 (%)	*p*-value[a]
Pre-existing Maternal Disease	8 (4.6)	5 (7)	3 (2.9)	0.275
Vaginal Bleeding not related to abruption	1 (0.6)	0 (0)	1 (1)	1
Worsening maternal condition due to COVID-19	8 (4.6)	1 (1.4)	7 (6.9)	0.143
Other[c]	14 (8.1)	6 (8.5)	8 (7.8)	0.885
Induction of Labor Fetal Indication				
Intrauterine Growth Retardation	5 (2.9)	2 (2.8)	3 (2.9)	0.666
Macrosomia	3 (1.7)	2 (2.8)	1 (1)	0.569
Non-Reassuring Fetal Heart Tracing (category 2 and 3)	3 (1.7)	0 (0)	3 (2.9)	0.27
Other[d]	4 (2.3)	2 (2.8)	2 (2)	0.544
Rupture of membranes				
Spontaneous	61 (35.3)	26 (36.6)	35 (34.3)	0.755
Artificial	81 (46.8)	20 (28.2)	61 (59.8)	**< 0.001**
Prolong Rupture of Membrane	2 (1.2)	0 (0)	2 (2)	0.513
Meconium Stain Amniotic Fluid	5 (2.9)	2 (2.8)	3 (2.9)	1
Route of delivery				
Vaginal	99 (57.2)	47 (66.2)	52 (51)	**0.047**
C-Section	74 (42.8)	24 (33.8)	50 (49)	
Preterm delivery (includes stillbirth delivery[f])	45 (26)	12 (16.9)	33 (32.4)	**0.023**
Route of Delivery for Preterm Deliveries (*n* = 47)				
Vaginal	14/47 (29.8)	5/12 (41.7)	9/35 (25.7)	0.465
C-Section	33/47 (70.2)	7/12 (58.3)	26/35 (74.3)	
Type of labor among vaginal preterm delivery (*n* = 14)				
Spontaneous	9/14 (64.3)	4/5 (80)	5/9 (55.6)	0.58
Induced	5/14 (35.7)	1/5 (20)	4/9 (44.4)	
Type of labor among c-section preterm delivery (*n* = 33)				
Spontaneous	30/33 (90.9)	6/7 (85.7)	24/26 (92.3)	0.523
Induced	3/33 (9.1)	1/7 (14.3)	2/26 (7.7)	
C-Section parsed by term and preterm; *n* = 74				
37 weeks or more	41/74 (55.4)	17/24 (70.8)	24/50 (48)	0.064
< 37 weeks	33/74 (44.6)	7/24 (29.2)	26/50 (52)	
Cesarean section; maternal indications				
Previous C-Section	32 (18.5)	14 (19.7)	18 (17.6)	0.73
Preexisting Maternal conditions[g]	6 (3.5)	6 (8.5)	0	**0.004**
Worsening maternal conditions[h]	31 (17.9)	8 (11.3)	23 (22.5)	**0.057**
Worsening maternal condition due to COVID-19	16 (9.2)	2 (2.8)	14 (13.7)	**0.016**
Labor Dystocia	8 (4.6)	3 (4.2)	5 (4.9)	1
Cesarean section; fetal indications				
Non-Reassuring Fetal Heart Tracing or rate	26/33 (78.8)	7/13 (53.8)	19/20 (95)	**0.008**
Fetal Malpresentation	5/33 (15.2)	5/13 (38.5)	0 (0)	**0.005**
Other[i]	2/33 (6.1)	1/13 (7.7)	1 (5)	1
Postpartum Complication				
Postpartum Hemorrhage	5 (2.9)	3 (4.2)	2 (2)	0.402
Hemorrhage required blood transfusion	3 (1.7)	2 (2.8)	1 (1)	0.569
Infection/Fever	1 (0.6)	1 (1.4)	0 (0)	0.41
Hypertensive Disorder of Pregnancy	2 (1.2)	0 (0)	2 (2)	0.513
Worsening COVID status	11 (6.4)	2 (2.8)	9 (8.8)	0.203
Wound complication if C-Section	1 (0.6)	0 (0)	1 (1)	1
Other/ mastitis/ diabetes	6 (3.5)	3 (4.2)	3 (2.9)	0.69
Maternal Disposition				

Table 1 (continued)

Maternal characteristics & outcomes	Total study population *N* = 173	Pre-delta *n* = 71 (%)	Delta *n* = 102 (%)	*p*-value[a]
Discharge home	171 (98.8)	70 (98.6)	101 (99)	0.654
Transferred to another facility	2 (1.2)	1 (1.4)	1 (1)	

[a] *p*-value of < 0.05 is considered statistically significant

[b] Cholestasis, Gestational Diabetes Mellitus, Advanced Maternal Age, No Prenatal Care

[c] Spontaneous Rupture of Membrane, Fetal demise, Polyhydramnios

[d] Intrauterine Fetal Demise, Twins, Cord prolapse

[e] Abnormal umbilical Doppler & Fetal demise

[f] Earliest gestational age was 20 weeks

[g] Advanced maternal age, obesity, pre-existing disease

[h] Hypertensive disorder of pregnancy, abruption, vaginal bleeding- not abruption, DVT/thromboembolic event

[i] Patient transferred for ECMO and returned to facility prior to final disposition of home

Table 2 Maternal respiratory and medical support of COVID-19 infected hospitalized patients during the pre-delta and delta time periods

	Total study Population *N* = 173	Pre-Delta *n* = 71 (%)	Delta *n* = 102 (%)	*p*-value[¶]
Intensive Care Unit admission	16/163 (9.8)	3/61 (4.9)	13/102 (12.7)	0.172
Respiratory Support requirement				
None	147 (85)	68 (95.8)	79 (77.5)	**0.001**
Need for supplemental O2 or CPAP	18 (10.4)	1 (1.4)	17 (16.7)	
Ventilatory support	8 (4.6)	2 (2.8)	6 (5.9)	
Extra Corporeal Membrane Oxygenation	1/160 (0.6)	1/59 (1.7)	0 (0)	0.369
Medications				
Chloroquine	5 (2.9)	3 (4.2)	2 (2)	0.402
Antivirals*	28 (16.2)	4 (5.6)	24 (23.5)	**0.001**
Monoclonal antibodies[#]	3 (1.7)	0 (0)	3 (2.9)	0.27
Steroids for Fetal Indication	19 (11)	7 (9.9)	12 (11.8)	0.087
Steroids for Maternal Indication	26 (15)	7 (9.9)	19 (18.6)	0.112
Antibiotics	33 (19.1)	13 (18.3)	20 (19.6)	0.847
Anticoagulants	17 (9.8)	3 (4.2)	14 (13.7)	**0.042**
Other	9 (5.2)	3 (4.2)	6 (5.9)	0.739

¶ *p*-value of < 0.05 is considered statistically significant

* remdesivir

Regeneron

There was a longer mean (7.1 days, 9.9 days; $p<0.001$) and median (2 days, 3 days; $p<0.001$) length of stay for liveborn babies in the Delta time period. When stratified by term and preterm, this difference in median length of stay was due to the disparity in the length of stay of the term liveborn babies (2 day, 3 days; $p<0.001$). In comparing the term newborns between both groups, there were no differences in Apgar scores at one or five minutes, need for delivery room resuscitation, or maximum respiratory support between groups.

There was a higher rate of small for gestational age (SGA) liveborn babies in the pre-Delta group (12.7%, 1%; $p=0.001$). When parsed by term and preterm, this difference was still significant in the term babies (11.9%, 1.4%; $p=0.008$), but not the preterm groups.

Newborn testing decreased during the Delta time period (73.2%, 37.0%; $p<0.001$). Of the newborns who were tested for SARS-CoV-2 virus, only 5 newborns (5.5% of tested babies) were polymerase chain reaction-positive. The Delta group did have a higher, but statistically insignificant positivity rate (1.9%, 10.3%; $p=0.08$). There was one COVID-19 positive preterm baby, born in the pre-Delta time period, that required NICU care. The pre-Delta infant (930 gram 26-weeks preterm-AGA) was SARS-CoV-2 RNA Qualitative (Rapid ID Now (Abbott Diagnostics, Scarborough, Inc.) positive at 1, 3 and 7 days of age, and tested negative at 16 days of age. Her SARS-CoV-2 Serology (COVID-19) Antibody (IgG, IgM) Immunoassay testing at 6 days of age was negative for COVID-19 antibodies, and she was discharged at 66 days of age in room air; grade 1 intraventricular hemorrhage, stage 1 retinopathy of prematurity, and never felt to demonstrate any signs or lab findings suggestive of perinatal infection. The other 4 COVID-19 positive infants were all

Table 3 Logistic regression model for predictors of preterm delivery

Predictors of preterm delivery	β	95% C.I.	*p*-value *
Pre-Delta	**Reference**		
Delta	0.862	(0.759–7.381)	0.137
Diagnosed > 30 days prior to delivery	**Reference**		
Diagnosed within 1–14 days prior to delivery	0.968	(0.679–10.212)	0.161
Diagnosed within 15–30 days prior to delivery	1.524	(0.887–23.739)	0.069
Vaginal	**Reference**		
C-section	-0.581	(0.156–2)	0.371
Use of Antiviral agent during pregnancy	0.689	(0.442–8.972)	0.37
Use of Anticoagulants during pregnancy	-1.247	(0.036–2.294)	0.239
C/S secondary to maternal pre-existing condition†	1.969	(0.453–113.159)	0.162
C/S secondary to worsening condition‡	2.665	(3.328–62.027)	< 0.001
Artificial rupture of membranes	0.253	(0.468–3.542)	0.624

*p-value of < 0.05 consider statistically significant

† Maternal pre-existing condition: Advanced maternal age, obesity, and maternal disease

‡ Maternal Worsening condition: Pregnancy-induced hypertension, pre-eclampsia, abruption, vaginal bleeding not related to abruption, due to COVID-19, deep vein thrombosis

born at term (37–40 weeks) during the Delta time period. They were appropriate for gestational age, asymptomatic and discharged home with the mother.

There was no difference in Apgar scores, NICU admissions or need for respiratory support between time periods. Among all newborns, we did not identify any clinical indicators that suggested a suspicious or definitive case of perinatal COVID-19 transmission.

Discussion

Since the emergence of the SARS-CoV-2 wild type in late 2019, there have been resurgences in cases associated with multiple different variants. [17] The Delta variant (B.1.617), first reported in India in October 2020, led to a rise in cases and increased mortality and morbidity indicators in pregnant women [20]. Spain also experienced a second wave in the summer of 2020, resulting in more maternal hospitalizations but fewer hospital days, intensive care unit (ICU) days, and deaths [21]. The United Kingdom saw a second wave from September 2020 to January 2021, with more severe maternal infections [22]. However, obtaining accurate national assessments of maternal illness severity has been challenging due to inconsistent and limited data on ICU admissions and ventilatory support [14].

The Delta variant has had a significant impact on perinatal outcomes, more so than other variants [9, 17, 23]. There has been limited research describing the relative effects of the Delta variant on pregnant women. In our review of the literature, we found eight studies comparing the Delta variant to previous variants [10, 15, 16, 24–28]. These studies consistently showed increased severity of illness and ICU admissions in pregnant women with the Delta variant. One study conducted at Parkland Hospital in Dallas, Texas, found that the Delta variant was associated with increased maternal illness severity and the need for respiratory support [26]. Most of these studies found low vaccination rates among COVID-19 infected mothers. Goklu [27] reported 0% vaccination rates for pre-Delta and Delta time period patients and Seasely [10] found 0% and 3% vaccination rates for these time periods. Our study further supports the evidence that the Delta variant worsened perinatal outcomes in pregnant women with COVID-19.

In our study, we found that 19.6% of mothers were symptomatic upon admission, with a higher number of symptomatic mothers in the pre-Delta time period ($p=0.039$). Vousden did report more symptomatic patients in their Delta group [28].

During the Delta time period, there was an increased use of antiviral and anticoagulant therapies in our patients. This may suggest increased acuity of maternal illness or simply reflect the differences in availability of pharmaceuticals as well as management, with the greater use of protocols and increased awareness of thrombotic risk during the Delta time frame. Others also reported increased use of anticoagulant therapy in symptomatic patients with the Delta variant [28].

Our eligibility criteria included a diagnosis of COVID-19 occurring anytime during the pregnancy and within 10 days after delivery. Most of our cohort (65.3%) was diagnosed with COVID-19 within 14 days before, to 10 days after delivery. The Delta group had more mothers diagnosed 1–14 days before delivery compared to our pre-Delta cohort (33.8%, 57.8%, $p=0.002$). Hudak reported an association with preterm deliveries in mothers symptomatic in pre-Delta patients with COVID-19 diagnosis <= 14 days before delivery [12]. Although we did not find an independent risk for preterm delivery based on timing of diagnosis, it is logical to assume that proximity to delivery and severity of illness would negatively impact pregnancy outcomes.

The risk of preterm livebirths was also increased during the pre-Delta time period, as reported by the CDC for March-October 2020 and Hudak, based upon a national registry, ending March 2021, reported an overall 15.6% of newborns born preterm [6, 12]. A review article focused on neonatal exposure to COVID-19, again drawing from the pre-Delta literature, also found a higher

Table 4 COVID-19 pregnancy: neonatal characteristics: Jan 2020 -Nov 2021

Neonatal baseline characteristics and outcomes		Total *N* = 176[↑]	Pre-Delta *N* = 72	Delta *N* = 104	*p* – Value[a]
Birthweight, mean (SD),*n* = 171		3033 (± 653) (49)	3109 (± 676) (80)	2978 (± 634) (63)	0.08
Birthweight, median (IQR),*n* = 171		3145 (2707–3430)	3260 (2760–3580)	3100 (2671–3398)	0.08
Length of Stay (days), median (IQR)[b], *n* = 171		3 (2–4)	2 (1–3)	3 (3–4)	**< 0.001**
Length of Stay (days), mean		8.75	7.1	9.92	**< 0.001**
Length of Stay (days), median (IQR)[b], *n* = 171					
	>= 37 weeks	2 (2–3)	2 (1–2)	3 (2–3)	**< 0.001**
	< 37 weeks	18.5 (4–30.5)	22.5 (3–59)	18 (4–29)	1
Length of Stay (days), mean					
	>= 37 weeks	2.98	2.75	3.19	0.532
	< 37 weeks	26.45	28.5	25.63	0.793
Birth Facility					
	Healthpark	135/176 (76.7)	56/72 (77.8)	79/104 (76)	0.779
	Cape Coral hospital	41/176 (23.3)	16/72 (22.2)	25/104 (24)	
Infants Care site[b]					
	Mother: Baby Unit	137/171 (77.8)	58/71 (81.7)	79/100 (79)	0.664
	NICU	34/171 (19.3)	13/71 (18.3)	21/100 (21)	
Respiratory support status on NICU Admission/ Transfer					
	None	13/34 (38.2%)	6/34 (46.2%)	7/21 (33.3%)	0.455
	Yes	21/34 (61.8%)	7/34 (53.8%)	14/21 (66.7%)	
Neonatal Disposition/ Outcome					
	Well baby nursery	137/176 (77.8)	58/72 (80.6)	79/104 (76)	0.471
	NICU admission/ Fetal Death	39/176 (22.2)	14/72 (19.4)	25/104 (24)	
Gender[b]					
	Male	87/171 (50)	38/71 (52.8)	50/100 (50)	0.719
	Female	84/171 (47.7)	34/71 (47.2)	50/100 (50)	
Ethnicity (of mother)					
	Hispanic	76/176 (43.2)	36/72 (50)	40/104 (38.5)	0.129
	Non Hispanic	100/176 (56.8)	36/72 (50)	64/104 (61.5)	
Race					
	Asian	1/176 (0.6)	1/72 (1.4)	0/104 (0)	0.065
	Black	23/176 (13.1)	11/72 (15.3)	12/104 (11.5)	
	White	139/176 (79)	51/72 (71.8)	88/104 (84.6)	
	None of the above	13/176 (7.4)	9/72 (12.5)	4/104 (3.8)	
Gestational Age group at birth (live birth)[b]					
	≥ 37 weeks	129/171 (75.4)	59/71 (83.1)	70/100 (70)	**0.05**
	< 37 weeks	42/171 (24.6)	12/71 (16.9)	30/100 (30)	
Gestational Age group					
	35–36 weeks	18/47 (38.3)	5/13 (38.5)	13/34 (38.2)	0.725
	31–34 weeks	18/47 (38.3)	4/13 (30.8)	14/34 (41.2)	
	27–30 weeks	4/47 (8.5)	2/13 (15.4)	2/34 (5.9)	
	≤ 26 weeks	7/47 (14.9)	2/13 (15.4)	5/34 (14.7)	
APGAR					
@ 1 min	**≥ 7**	154/171 (90.1)	67/71 (94.4)	87/100 (87)	0.128
	< 7	17/171 (9.9)	4/71 (5.6)	13/100 (13)	
@ 5 min	**≥ 7**	161/171 (94.5)	67/71 (94.4)	94/100 (94)	1
	< 7	10/171 (5.8)	4/71 (5.6)	6/100 (6)	
APGAR: >= 37 weeks GA					
@ 1 min	**≥ 7**	123/129 (95.3)	58/59 (98.3)	65/70 (92.9)	0.218
	< 7	6/129 (4.7)	1/59 (1.7)	5/70 (7.1)	
@ 5 min	**≥ 7**	125/129 (96.9)	58/59 (98.3)	67/70 (95.7)	0.625
	< 7	4/129 (3.1)	1/59 (1.7)	3/70 (4.3)	
APGAR: < 37 weeks GA					

Table 4 (continued)

Neonatal baseline characteristics and outcomes		Total $N=176^{\dagger}$	Pre-Delta $N=72$	Delta $N=104$	p – Value[a]
@ 1 min	**≥ 7**	31/42 (73.8)	9/12 (75)	22/30 (73.3)	1
	< 7	11/42 (26.2)	3/12 (25)	8/30 (26.7)	
@ 5 min	**≥ 7**	36/42 (85.7)	9/12 (75)	27/30 (90)	0.329
	< 7	6/42 (14.3)	3/12 (25)	3/30 (10)	
Multiplicity[b]					
	Singleton	165/171 (96.5)	69/71 (97.2)	96/100 (96)	1
	Twin Gestation	6/171 (3.5)	2/71 (2.8)	4/100 (4)	
Growth[b]					
	AGA[c]	153/171 (89.5)	57/71 (80.3)	96/100 (96)	**0.001**
	SGA[d]	10/171 (5.8)	9/71 (12.7)	1/100 (1)	
	LGA[e]	8/171 (4.7)	5/71 (7)	3/100 (3)	
In Utero Growth in ≥ 37 weeks					
	AGA	116/129 (89.9)	48/59 (87.4)	68/70 (97.1)	**0.008**
	SGA	8/129 (6.2)	7/59 (11.9)	1/70 (1.4)	
	LGA	5/129 (3.9)	4/59 (6.8)	1/70 (1.4)	
In Utero Growth in < 37 weeks					
	AGA	37/42 (88.1)	9/12 (75)	28/30 (93.3)	0.095
	SGA	2/42 (4.8)	2/12 (16.7)	0/30 (0)	
	LGA	3/42 (7.1)	1/12 (8.3)	2/30 (6.7)	
DR#Resuscitation					
	None / Basic[f]	122/171 (71.3)	51/71 (71.8)	71/100 (71)	0.906
	Yes[g]	49/171 (28.7)	20/71 (28.2)	29/100 (29)	
DR#Resuscitation: ≥ 37 weeks					
	None / Basic	105/129 (81.4)	46/59 (78)	59/70 (84.3)	0.358
	Yes	24/129 (18.6)	13/59 (22)	11/70 (15.7)	
DR#Resuscitation: < 37 weeks					
	None / Basic	17/42 (40.5)	5/12 (41.7)	12/30 (40)	1
	Yes (O2 or greater)	25/42 (59.5)	7/12 (58.3)	18/30 (60)	
Neonatal COVID-19 Testing					
	Tested	89/171 (52)	52/71 (73.2)	37/100 (37)	**< 0.001**
	Not Tested	82/171 (48)	19/71 (26.8)	63/100 (63)	
Neonatal COVID-19 Test Results					
	Negative	85/91 (93.4)	51/52 (98.1)	34/39 (87.2)	0.08
	Positive	5/91 (5.5)	1/52 (1.9)	4/39 (10.3)	
Maximum Respiratory Support Required[b]					
	None	149/171 (87.1)	63/71 (88.7)	86/100 (86)	0.599
	Oxygen/ CPAP/ Ventilator	22/171 (12.9	8/71 (11.3)	14/100 (14)	

[a] p-value of < 0.05 is considered statistically significant

[b] Five fetal demise patients excluded

[c] Appropriate for Gestational Age

[d] Small for Gestational Age

[e] Large for Gestational Age

[f] None or Warm, Dry, Suction

[g] BlowBy Oxygen/ Continuous Positive Airway Pressure / Positive Pressure Ventilation (PPV)

Mann-Whitney U test used to compare median BW and Length of Stay

rate of premature delivery which was related to maternal conditions, and not an increase in spontaneous preterm labor [29]. Most significantly, our study found this risk for preterm delivery and liveborn preterm delivery to be increased during the Delta time period.

In our cohort, there was a greater use of artificial rupture of membranes in the Delta group (28.2%,59.8%; $p<0.001$) which may reflect a more active management approach by the obstetrician. Univariate analysis identified "'worsening maternal condition due to COVID-19" (2.8%,13.7%; p=0.016), to be a greater risk factor in our

Delta group, and "worsening maternal condition" overall was an independent risk factor for preterm delivery (β=2.66, 3.32–62.02, p<0.001). Our small sample size may have been insufficiently powered to demonstrate an independent risk of COVID-19. Speculatively, worsening maternal condition associated with COVID-19 infection may be associated with a need for more active management, including early delivery.

The Delta group also had a higher overall rate of c-section (33.8%,49%; $p=0.047$). Others have also reported higher rates of cesarean section during the Delta periods [10, 27]. Our study showed a significant increase in both maternal and fetal indications for cesarean section during the Delta period. In addition, there was a higher indication for cesarean section due to non-reassuring fetal status suggesting higher risk for fetal compromise in the Delta cohort.

DeSisto, in a CDC report on national outcomes, compared defined pre-Delta (March 2020-June 2021) to Delta (July-September 2021) time periods and found increased risk of stillbirths with COVID-19 infection during pregnancy, as well as accentuated risk during the Delta variant time period [30]. Nationally, for COVID-19 positive pregnancies, the stillbirth rate (March 2020 through September 2021) was 12.6/1000 birth; the national population stillbirth rate for the same time period was 6.5/1000 births (adjusted relative risk=1.90; 95% CI=1.69–2.15). COVID-19 positive pregnancy stillbirth rates worsened during the Delta time period: pre-Delta 9.8/1000 births compared to a Delta stillbirth rate of 27.0/1000 births (aRR=4.04; 95% CI=3.28–4.97) [30].

Our study's overall COVID-19 cohort stillbirth rate (January 2020 to November 2021) was 28.4/1000 live births which was significantly higher as compared to our local overall population stillbirth rate which was comparable to the reported national rate at 6.5/1000 live births (5/171, 89/13,539; $p=0.006$). Our comparative COVID-19 positive pregnancy stillbirth rates suggest a higher risk during the Delta time period: Pre-Delta 13.9/1000 births compared to a Delta stillbirth rate of 38.5/1000 births ($p=0.65$). Recent literature implicates a pathophysiologic mechanism associated with placental insufficiency rather than a direct viral effect on the fetus [31–33]. A stillbirth outcome could be an end marker for this effect. In one recent case report an intrauterine fetal demise was described in a Delta variant infected patient with mild symptoms found to be associated with placental malperfusion due to cytokine storm [32]. This is in line with other evidence suggesting a direct effect on the placental, as opposed to the fetus, and may offer an explanation for the increased stillbirths seen during the Delta surge and in COVID-19 infected pregnancies overall.

Although there is a risk for perinatal COVID-19 transmission, most of the newborn acquisition has been post-natal. The short-term impact of maternal COVID-19 on the newborn appears primarily related to an increased risk for preterm birth, and the direct consequences of prematurity [12, 29].

The newborns in the Delta group did have a slightly longer length of stay. Although the Delta group had more preterm births, the difference in length of stay was attributable to the term babies. In this sub-group we did not find any difference in Apgar scores, need for delivery room resuscitation, or need for respiratory support.

Although we did not find any difference in mean birthweights, when viewed by Fenton growth categories, there were more SGA liveborn births to women with COVID-19 during pregnancy in the pre-Delta group. Interestingly, this growth disparity was significant only in the term baby subgroup, and not so in the preterm subgroup. Women who acquire COVID-19 may be at risk for intrauterine growth retardation [29], or some degree of in utero growth faltering and possibly dependent on the timing of exposure to the virus. If maternal COVID-19 has a pathophysiologic effect due to direct placental compromise, it is reasonable to surmise that any impact of the maternal infection on the fetus will be linked to the timing of acquisition, and duration of exposure. Our study demonstrated a difference in viral acquisition between groups. Speculatively, a higher rate of earlier deliveries, as was occurring in the Delta group, might result in delivery before the growth discrepancy became measurable at term. However, Wallace did report comparative data between their pre-Delta and Delta cohorts, with no difference in median length of stay, a greater incidence of SGA babies in the Delta group (3.32%, 6.19%), and an increased but comparable preterm delivery rate (28.04%, 25.66%) [35].

The strength of our study is the utilization of local data resources and chart reviews for accurate assessment of outcomes. The study periods were based on prevailing epidemiologic trends and the emergence of the Delta variant. In determining our study time epochs, we did not have availability of laboratory sequencing to confirm the presence of the SARS-CoV-2 Delta variant (B.1.617.2). Although we listed January 2020 as our start date for data collection purposes, our earliest eligible patient was in April 2020. Our earliest mother: baby dyad identified, i.e. born prior to our first included birth, was excluded from the study due to nosocomial maternal acquisition - born on March 18, 2020 and was a 33 week preterm infant who did develop late-onset neonatal COVID-19 symptoms after maternal onset 19 days after delivery [36]. We determined the end date of our review based upon decreasing overall COVID-19 positive admissions, as well as when the Omicron variant was emerging.

This is a descriptive comparison of two time periods, limited to hospitalized mothers with a delivery outcome

and with a historical or known diagnosis of COVID-19 during pregnancy. For diagnosis based upon maternal recollection/ history in addition to physical assessment and confirmatory lab testing, we might not have identified the asymptomatic mothers with an undisclosed diagnosis of COVID-19 during their pregnancy This risk of missing the diagnosis might increase with infections that occur earlier in pregnancy. With greater awareness of COVID infections by the Delta time period, any potential bias would have no effect, or favor a larger denominator during the Delta time period, and thus increased likelihood of finding no difference. Of note, there was no difference in our pre-Delta and Delta time periods for COVID-19 diagnosis > 30 days before delivery.

We are not able to control for evolving local practices and infectious disease recommendations over time. Presuming that changing practice implies improved management during the Delta time period, this again would favor a type 2 error, finding no difference between the pre-Delta and Delta time periods.

Our study time periods overlapped with the availability of COVID-19 vaccines, which may have influenced the severity of illness. National estimates suggest that from December 2020 to May 2021, 16.3% of pregnant women had received at least one dose of a COVID vaccine [37]. Trended national statistics for pregnant women ages 18–49 years, show completion of the primary series of COVID-19 vaccine from December 2020 to June 2021 increased from 0 to 42%, and from July 2021 to November 2021 increased from 45–66% [38]. Given that vaccine exposure tends to decrease severity of illness, need for hospitalization and death, the direction of bias, again, would be towards decreased ability to demonstrate a difference in severity of illness, highlighting the clinical importance of our positive findings.

Our findings support a true difference in maternal outcomes during the Delta time period. A major limitation of our study is a small sample size and the risk of type 2 errors. A larger study would likely confirm our findings and clarify some of the suggested differences.

Conclusions

In a public, non-profit health system, from January 2020 to November of 2021, mothers with a diagnosis of COVID-19 during pregnancy, exhibited more preterm deliveries during the Delta time period, as well as longer length of stay for liveborn babies. For the entire cohort, there was an increased risk of stillbirths and preterm deliveries with COVID-19 infection compared to the general population.

Abbreviations

ROM	Rupture of membranes
AROM	Artificial rupture of membranes
IOL	Induction of labor
c-section	Cesarean section
ICU	Intensive care unit
ECMO	Extracorporeal membrane oxygenation
GA	Gestational age
BW	Birth weight
SGA	Small for gestational age
AGA	Appropriate for gestational age
LGA	Large for gestatonal age
DR	Delivery room
LOS	Length of stay

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Author contributions

CM and WFL conceived and designed the study. WFL wrote the main manuscript text and CM and HD substanially modified it. CM, HD and WFL analyzed and interpreted the data. CM, HD and WFL critically reviewed and revised drafts and all approved of the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

The study was approved by the Lee Health Institutional Review Committee.

Consent for publication

Not applicable as the study utilized a deidentified dataset.

Competing interests

The authors declare no competing interests.

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