

**IMPACT OF THE COVID-19 PANDEMIC ON EXCESS PERINATAL  
MORTALITY AND MORBIDITY IN ISRAEL**

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**Key Words:** APGAR, birthweight, cesarean section, COVID 19, pandemic, preterm, post-date, IUFD, SARS-COV-2, stillbirth, umbilical-pH.

**Word Count:** 2320 (Text); 239 (Abstract)

**Declarations of interest:** Authors reports no conflict of interest.

**Funding:** None Received

**Short Title:** COVID-19 pandemic and stillbirth.

**Condensation:** The first wave of the COVID-19 pandemic in Israel was associated with less prenatal emergency labour ward admission and more stillbirth.

**AJOG at a Glance:**

**A.** Why was this study conducted?

- The 2020 COVID-19 pandemic led to major restrictions on travelling and gathering, which may have compromised obstetrical care as well.
- This study was conducted to evaluate the influence of the first wave of the COVID-19 pandemic on prenatal emergency labour ward admission and perinatal outcomes.

**B.** What are the key findings?

- During the peak of the COVID-19 2020 pandemic there were less prenatal emergency labour ward admission and more cases of stillbirth compared to the combined corresponding periods in the years 2017-2019.

**C.** What does this study add to what is already known?

- Fear of catching the infection and/or stay-at-home instructions during the pandemic peak lead to delayed care.
- Higher stillbirth rate can be considered as a collateral damage of the COVID-19 pandemic in non-infected pregnant women.

## **Abstract**

**BACKGROUND:** The 2020 COVID-19 pandemic has been associated with excess mortality and morbidity in adults and teenagers over 14 years of age but there is still limited evidence on the direct and indirect impact of the pandemic on pregnancy.

**OBJECTIVE:** We aimed to evaluate the effect of the first wave of COVID-19 pandemic on obstetrical emergency attendance in a low-risk population and the corresponding perinatal outcomes.

**MATERIAL AND METHODS:** This is a single center retrospective cohort study of all singleton births between February 21st and April 30th. Prenatal emergency labour ward admission numbers and obstetric outcomes during the peak of the first COVID-19 pandemic in Israel were compared to the combined corresponding periods for the years 2017-2019.

**RESULTS:** During the 2020 COVID-19 pandemic, the mean number of prenatal emergency- labour ward admission was lower, both by daily count and per woman, in comparison to the combined matching periods in 2017, 2018 and 2019 ( $48.6 \pm 12.2$  vs  $57.8 \pm 14.4$ ,  $p < .0001$  and  $1.74 \pm 1.1$  vs  $1.92 \pm 1.2$ ,  $p < .0001$ , respectively). A significantly ( $p = .0370$ ) higher rate of stillbirth was noted in the study group (0.4%) compared to the control group (0.1%). All study group patients were negative for COVID-19. Gestational age at delivery, rates of premature delivery at  $< 28$ ,  $34$  and  $37$  weeks, pregnancy complications, post-date delivery at  $> 40$  and  $41$  weeks, mode of delivery and numbers of emergency cesarean deliveries were similar in both groups. There was no difference in the intrapartum fetal death rate between the groups.

**CONCLUSION:** The COVID-19 pandemic stay-at-home policy combined with patient's fear of contracting the disease in hospital could explain associated the higher rate of stillbirth. This collateral perinatal damage follows a decreased in prenatal emergency labour ward admission during the first wave of COVID-19 in Israel.

## Introduction

Excess deaths due to coronavirus disease (COVID-19) following the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in China in late December 2019 is now well documented. Pooled estimates of all-cause mortality for 24 European countries/federal states participating in the European monitoring of excess mortality for public health action (EuroMOMO) network, for the period March–April 2020 have shown excess mortality in all age groups > 14 year olds<sup>1</sup>. In Israel, the first COVID-19 case was diagnosed on 21 February 2020 and from the beginning of March onwards strict restrictions on movement and gathering were imposed. On 11 March 2020, COVID-19 was declared a pandemic by the World Health Organization (WHO)<sup>2</sup> and on 23 March full lock-down was imposed in Israel.

The importance of routine obstetrical care is well established, especially in high risk pregnancies and health authorities around the world issue have issued instructions and guidance for antenatal and perinatal care not to be disrupted during the COVID-19 pandemic. The identification of pregnant women needing rapid interventions, including induction of labor or emergency cesarean section, is considered as critical as interventions cardiovascular emergencies<sup>3–6</sup>. Furthermore even if most pregnant women infected with COVID-19 only develop mild or moderate symptoms<sup>7–10</sup>, early reports published in April and May 2020 showed that women in the third-trimester of gestation were at higher risk for critical illness<sup>7</sup> and preterm cesarean delivery for maternal indications<sup>10–12</sup>.

Recent studies have shown that most neonates born to infected mother are asymptomatic, and there is only limited evidence suggesting vertical transmission<sup>7,8,11,13</sup>. A small case series of five stillbirths in infected mother from Brazil has suggested that secondary chorioamnionitis due to COVID-19 as the cause for fetal death<sup>14</sup>. A population-based descriptive study using the UK Obstetric Surveillance System (UKOSS) has reported 2.5-fold increase in incidence of stillbirth at the beginning of the pandemic

compared the national rate in 2019<sup>15</sup>. A more recent study from one centre in the UK comparing the changes in incidence of stillbirth and preterm birth has also found an increase in stillbirth between February 1<sup>st</sup> and mid-June 2020 compared to October 1<sup>st</sup> 2019 and January 31<sup>st</sup> 2020<sup>16</sup>. However, as there is a seasonal impact on births and stillbirths<sup>17,18</sup>, the comparison of different periods of the year may have skewed the data in both studies.

For a short period of time, at the start of the pandemic, access to antenatal clinics was limited due to the need for maternity services to put in place special measures required to prevent nosocomial transmission of COVID-19 and medical staff shortage due to self-isolation after exposure to an infected patient or relative. In addition, and similarly to other medical specialities such cardiovascular diseases<sup>3-6</sup>, pregnant women's fear of contracting infection during a hospital visit must have had an impact on prenatal consultation attendance. In the present study we have evaluated the effect of the first peak of the COVID-19 pandemic in Israel on prenatal care and obstetrical outcomes compared to the same periods for the year 2017, 2018 and 2019.

## **Materials and Methods**

This is a retrospective cohort study of the prenatal care and obstetrical outcomes between February 21<sup>st</sup> and April 30<sup>th</sup>, 2020, compared to the same period of the year in 2017, 2018 and 2019.

### **Study population**

All pregnant women with singleton gestation admitted during the COVID-19 peak period (study group) and the corresponding period in 2017-2019 (control group) to the labor ward in Shamir Medical Center (Zerifin, Israel), which is a tertiary, university-affiliated hospital, with about 9000 deliveries per a year were included in the study. Premature pre-viable

deliveries < 24 weeks, multiple pregnancies and deliveries following feticide were excluded from the study groups.

Demographic, obstetrical, and neonatal data were retrieved from computerized medical records and the hospital's laboratory database. Data collected for each participant included maternal age, gravidity, parity, and previous cesarean deliveries. Obstetrical and neonatal data collected included, induction of labor, mode of delivery and indication for cesarean delivery if preformed, date and time of birth, APGAR score at 5 minutes, arterial umbilical cord pH, neonatal intensive care unit (NICU) admission and perinatal mortality. For stillbirth cases, stillbirth-weight percentiles were calculated according to nationally accepted growth curves for gestational week and gender<sup>19</sup>. In addition, the following were reviewed: maternal COVID-19 test results at admission, presence of meconium stained or bloody amniotic fluid at the time of membrane rupture, pregnancy follow up, placental and umbilical cord abnormalities as examined by the department of pathology, and fetal dysmorphism as noted in the labor ward following obstetric and midwife examination after delivery.

The primary outcome was fetal death, categorized into antepartum (stillbirth) or intrapartum. Secondary outcomes were gestational age at birth, maternal diabetes, maternal pregnancy induced hypertension, induction of labor, mode of delivery, type of cesarean delivery (elective, non-elective, or intra-partum), birth weight, 5-minute APGAR score, umbilical artery cord pH, and NICU admission.

The study was approved by the local institutional review board (approval no. 0134-20-ASF). Informed consent was waived due to the retrospective design of the study.

### Statistical analysis

The SAS (SAS Cooperation, Version 34.0, North Carolina, USA) data analysis and statistical software package was used to analyze the data. A standard Kurtosis analysis indicated that the values were normally distributed, and the data are therefore continuous

variables presented as mean and standard deviation. Categorical variables are presented as count and percentages. Pearson  $\chi^2$  test or Fisher-exact, as appropriate, were used to compare between the study and control groups with respect to categorical variables. Independent samples t-test was used to compare the means of the 2 groups for continuous variables. All p-values were determined with two-tailed tests. A *P* value of  $<.05$  was considered statistically significant.

## Results

There were 1556 birth registered during first wave of the COVID-19 pandemic. The control group included 1578, 1545 and 1441 newborns that were delivered during the same period of the year in 2017, 2018 and 2019 respectively (Figure 1).

Maternal age, race/ethnicity, the rate of prior cesarean deliveries, maternal diabetes and hypertensive rates were all similar between groups (Table 1). The mean gravidity and parity were increased in the study group ( $3.0\pm 2.0$  vs  $2.7\pm 1.7$ ,  $p<.0001$ ;  $1.5\pm 1.6$  vs  $1.3\pm 1.3$ ,  $p<.0001$ ; gravidity and parity, for the study and control groups, respectively), and the nulliparity rate did not differ between groups ( $30.2\%$  vs  $32.2\%$ ,  $p=.1484$ ).

During the 2020 COVID-19 pandemic, the average number of prenatal emergency labour ward admission was lower, both by daily count and per woman, in comparison to the combined corresponding periods in 2017-2019 ( $48.6\pm 12.2$  vs  $57.8\pm 14.4$ ,  $p<.0001$ ;  $1.74\pm 1.1$  vs  $1.92\pm 1.2$ ,  $p<.0001$ , respectively) (Figure 2).

A significantly ( $p=.370$ ) higher rate of stillbirth was found in the study group ( $6/1556$ ,  $0.4\%$ ) compared to the control group ( $5/4564$ ,  $0.1\%$ ). There was no difference in the mean gestational age at the diagnosis of fetal death or the post-delivery stillbirth mean weight between study and control groups ( $35.7\pm 5.2$  vs  $36.2\pm 5.0$ ,  $p=.8969$ ;  $2074\pm 987$ g vs  $2633\pm 1066$ g,  $p=.4338$ ; gestational weeks at fetal-death diagnosis and stillbirth weight,

study and control groups respectively). Women in both groups self-referred for medical evaluation after either experiencing decreased fetal movements or contractions. A stillbirth was diagnosed in absence of fetal heartbeat on ultrasound examination. Women were delivered either vaginally or by cesarean section depending on obstetrical indication. All the women who experienced stillbirth in the study group were tested and found negative for COVID-19.

In five out of the total 11 cases stillbirths recorded in the study and control groups, histopathology findings were suggestive of placental insufficiency. In three of these cases in study group the fetal birth weight was below the 10<sup>th</sup> centile for gestational age whereas in the controls one stillbirth presented with anhydramnios and one presented with both a birth weight below the 10<sup>th</sup> centile and anhydramnios. Histopathologic findings suggesting a cord accident as the cause of fetal death were found only in the study group including one case with a true knot of cord and the other with a pathological narrowing of a portion of the cord. One stillbirth from each group presented with blood in the amniotic fluid, suggesting a placental abruption. One stillbirth in study group was diagnosed with chorioamnionitis due to *Escherichia coli*. One case from the study group and two from the control group presented with meconium stained amniotic fluid. Two women from the control group had no pathological findings. Two women from the study group had previous stillbirth. All stillbirth infants were examined in detailed by the perinatal pathologist and none showed dysmorphic signs. None of the women who experienced stillbirth had neither diabetes nor hypertension.

One case of Intrapartum fetal death occurred in the control group but none were reported in the study group. (Table 2). Gestational age at birth, and rates of premature delivery at <28, 34 and 37 weeks, post-date delivery at > 40 and 41 weeks, mode of delivery and number of emergency cesarean delivery were similar in both groups. The induction of labor rate in the study group was higher compared to the control group (32.3%



vs 28.2% of all deliveries, study and control group respectively,  $p=0.0005$ ). The study group had more cases of 5-minute APGAR score lower than 7 (0.7% vs 0.3%,  $p=0.0214$ ), but the umbilical-artery pH and the neonatal-intensive-care-unit admission rates did not differ.

### Principal findings of the study

The data of our study indicate that the first wave of the COVID-19 pandemic was associated with a decline in pregnant women attendance to obstetrical emergency room which could explain a parallel increase in stillbirth rate compared to the same period in the previous 3 years. As all stillbirth cases in the present tested negative for COVID-19 virus, the higher stillbirth rate may be considered as a collateral damage from the stay-at-home mandates and fear of catching the virus in the hospital setting during the early stage of the pandemic.

### Comparison with existing literature

The COVID-19 pandemic has placed tremendous strain on health care systems worldwide across all medical specialities. From the start of the outbreak, many health care workers from different medical emergency specialities noticed a reduction in patient admissions for diseases not directly related to SARS-CoV-2 infections. In particular, a decline in the number of hospital admissions for acute coronary syndrome has been observed across Italy and USA during the peak of the COVID-19 pandemic, which correlates with higher mortality and morbidity<sup>3-6</sup>. A similar reduction in pediatric emergency department attendance with delayed treatment was also observed in Italy in March 2020 compared with previous years, resulting in poorer outcomes in many cases<sup>20</sup>.

By contrast to countries such as Italy, Spain, China and the US, the number of hospitalized patients with COVID-19 in Israel was relatively low and did not impact on the distribution of emergency medical services for non-COVID-19 related conditions<sup>21</sup>. Most healthcare resources were not relocated to manage the COVID-19 pandemic and in

particular there was no competing needs for equipment, and lack of beds in our hospital. Our data therefore suggest, that the decrease in prenatal emergency labour ward admission in our study was mainly due to the fear by pregnant women of contracting SARS-CoV-2, particularly after the media diffused the news that the infection was largely spread across hospitalized patients and healthcare personnel, due to the lack of personal protection equipment. This patient factor has been reported in previous pandemics<sup>9</sup> and may lead to pregnant women ignoring symptoms such as decreased fetal movements or not getting standard obstetrical care including regular glycaemic control or screening for hypertensive disorders which are known to be associated with higher stillbirth rate<sup>22,23</sup>.

### Clinical implications

Most women infected with Covid-19 are asymptomatic and national survey of the outcome of 427 pregnant women admitted to hospital with confirmed SARS-CoV-2 infection between 1 March 2020 and 14 April 2020 has found that 10% required intensive care support and 1% died<sup>15</sup>. SARS-CoV-2, outcomes are linked to various pre-existing comorbidities such as hypertension or diabetes and morbidity disproportionately affects those of lower socioeconomic status, and particularly ethnic minority<sup>24</sup>

The recent study by Khalil et al<sup>16</sup> found fewer nulliparous and showed both a decrease in the number of pregnant women with hypertension and an increase in the number of still birth at the start of the pandemic compared to the period immediately before. Our data confirm an increase in stillbirth at the peak of the COVID-19 pandemic in Israel i.e. February 21<sup>st</sup> and April 30<sup>th</sup>, 2020 compared the same periods of 3 consecutive years before accounting for the seasonal effect. By contrast we found, no differences maternal hypertension and nulliparity rates between. We also observed no difference in the premature delivery rates for any gestational periods at between 28 and 37 weeks, indicating that the increase in stillbirth rate was the main perinatal impact of the of the COVID-19 pandemic in Israel.

None of the women with pregnancies complicated by stillbirth included in the present study tested positive for COVID-19. Women from ethnic minorities account for less than 10% in our population which is much lower than UK<sup>16</sup> or the US. Although the rates of stillbirth increased significantly during the peak of the Covid-19 pandemic in our population it remain overall much lower than in the UK. These findings suggest that complications such as diabetes and hypertension which are more common in women from ethnic minorities did not influence the stillbirth rate in our study. Other confounding factors including as reduced mobility and exercise, increase smoking exposure, increased caloric intake, poor glycemic control for pre-gestational and gestational diabetic women, poor supervision and control of hypertensive complications, as well as uncontrolled thyroid disorders<sup>23,25</sup> could have indirectly contributed to risk of stillbirth during the lock-down.

### **Strengths and limitation of the study**

The strengths of our study lie in it being a from a single center, with uniform data documentation and clinical evaluation approach. In addition, to the best of our knowledge, this is the first study investigating the association between obstetrical care during the COVID-19 pandemic and stillbirth. The main limitation of our study is its retrospective design, with limited data available for some parameters. In addition, multiple gestations, which are a major risk factor for stillbirth, were excluded because of their relatively small number in this short period. Because of religious reasons the Israeli population often declines post-mortem autopsies, and therefore this information is limited to placental examination in both the study and control groups. However, all cases of stillbirth are examined externally by a trained perinatal pathologist and did not show evidence of fetal dysmorphism in both groups. A reduction in the community clinic activity greatly could have influenced the availability of medical services these data were not available.

## **Conclusions**

The COVID-19 pandemic is generation-defining global medical phenomenon, the scope, scale, and pace of which is unprecedented. Despite the limited impact of SARS-CoV-2 on pregnant women overall health, our data have shown a decrease in prenatal emergency labour ward admission parallel with an increase in the number of stillbirths during the first peak of the Covid-19 pandemic. This collateral damage was not due to a reduce access to our maternity services during that period but is more likely due to the patient fear of contracting the infection during hospital visits and like for other medical specialities may have discouraged them to access to emergency medical services during the first peak of the COVID-19 pandemic. These findings support government guidance in maintaining adequate emergency prenatal care during pandemic and in informing pregnant women about the need to attend routine prenatal consultation.

**Highlights:**

- The COVID-19 pandemic was associated with less attendance to obstetrical emergency room.
- A parallel increase in stillbirth rate was demonstrated with no changes in maternal diabetes or hypertension rates.
- All stillbirth cases during the pandemic tested negative for COVID-19 virus suggesting the influence of other factors.
- Stay-at-home mandates and pandemic panic are were the only identifiable for higher stillbirth rate.

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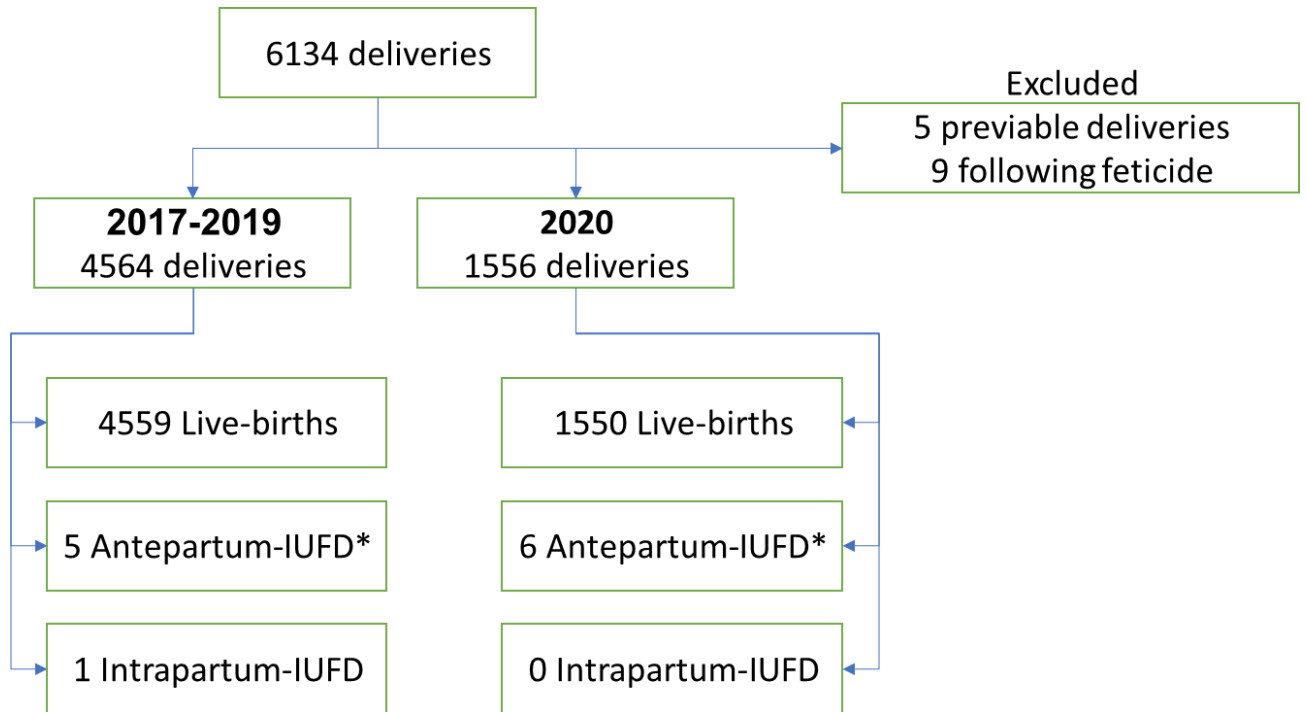


Figure 1 – Study flowchart. \* $p=0.0370$

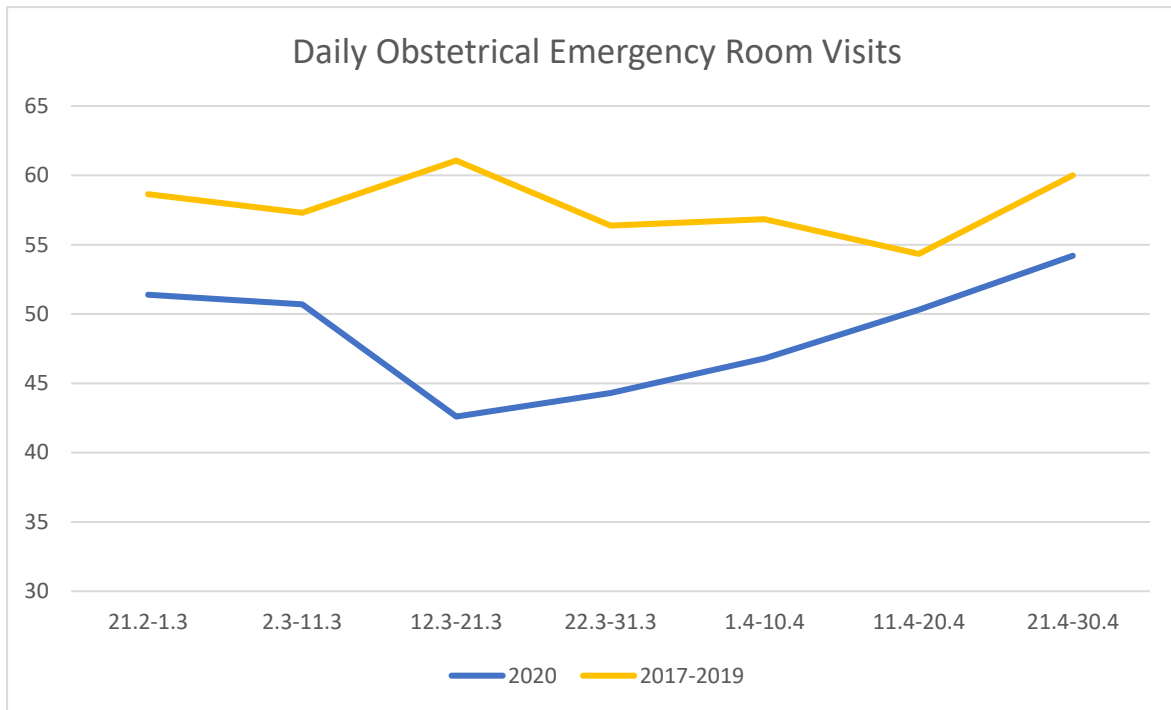


Figure 1 – Daily obstetrical room visits.  $P < 0.0001$ . For graphical purposes, data is presented in ten days average.

<b>Table 1 - Baseline demographic and clinical characteristics of study and control groups</b>			
<b>Characteristic</b>	<b>Study group</b>	<b>Control group</b>	<b>P-Value</b>
	<b>2020 (n=1556)</b>	<b>2017-2019 (n=4564)</b>	
Age (mean $\pm$ SD) years	30.8 $\pm$ 5.4	30.5 $\pm$ 5.3	0.1963
Gravidity (mean $\pm$ SD)	3.0 $\pm$ 2.0	2.7 $\pm$ 1.7	<0.0001
Parity (mean $\pm$ SD)	1.5 $\pm$ 1.6	1.3 $\pm$ 1.3	<0.0001
Number of nulliparous (%)	470 (30.2)	1468 (32.2)	0.1484
$\geq$ 1 previous cesarean delivery (n, %)	186 (12.0)	532 (11.7)	0.7510
Maternal diabetes (n, %)	109 (7.0)	371 (8.1)	0.1551
Maternal hypertension disorder (n, %)	49 (3.1)	181 (4.0)	0.1439
Ethnicity	White	1465 (94.2)	0.0967
	Others (Africans and Asians)	91 (5.8)	
SD = standard deviation;			

<b>Table 2 – Antepartum and intrapartum fetal death and associated factors in study and control groups</b>			
<b>Outcome</b>	<b>Study group</b>	<b>Control group</b>	<b>P-Value</b>
	<b>2020 (n=1556)</b>	<b>2017-2019 (n=4564)</b>	
Stillbirth (n, %)	6 (0.4)	5 (0.1)	0.0370
Gestational age at fetal-death diagnosis (weeks, mean $\pm$ SD)	35.7 $\pm$ 5.2	36.2 $\pm$ 5.0	0.8969

Stillbirth weight (grams, mean $\pm$ SD)	2074 $\pm$ 987	2633 $\pm$ 1066	0.4338
Stillbirth small for gestational age (n, %)	3/6 (50%)	1/5 (20%)	0.5455
Anhydramnios (n, %)	0/6 (0%)	2/5 (40%)	0.1818
Cord finding suggest potential cord accident (n, %)	2/6 (33%)	0/5 (0%)	0.4545
Blood stained amniotic fluid (n, %)	1/6 (17%)	1/5 (20%)	1.0
Meconium stain amniotic fluid (n, %)	1/6 (17%)	2/5 (40%)	0.5455
Chorioamnionitis (n, %)	1/6 (17%)	0/5 (0%)	1.0
Intrapartum intrauterine fetal death (n, %)	0 (0.0%)	1 (0.03%)	0.4804

n=number; SD = standard deviation;

**Table 3 - Perinatal Outcomes for study and control groups**

Outcome	Study group	Control group	p-Value	
	2020 (n=1556)	2017-2019 (n=4564)		
Gestational age at birth (weeks, mean $\pm$ SD)	39.32 $\pm$ 1.7	39.28 $\pm$ 1.7	0.4296	
Premature delivery <28 Gestational Weeks (n, %)	5 (0.3)	11 (0.2)	0.5922	
Premature delivery <34 Gestational Weeks (n, %)	17 (1.1)	51 (1.1)	0.9355	
Premature delivery <37 Gestational Weeks (n, %)	82 (5.3)	278 (6.1)	0.2345	
Post-date delivery >40 Gestational weeks (n, %)	530 (34.1)	1538 (33.7)	0.7937	
Post-date delivery >41 Gestational weeks (n, %)	135 (8.7)	346 (7.6)	0.1658	
Induction of labor (n, %)	502 (32.3)	1258 (28.2)	0.0005	
Mode of delivery	Spontaneous vaginal delivery (n, %)	1184 (76.1)	3473 (76.1)	0.9656
	Vacuum assisted vaginal delivery (n, %)	99 (6.4)	283 (6.2)	
	Cesarean delivery (n, %)	273 (17.5)	809 (17.7)	
Type of cesarean delivery	Elective (n, %)	91 (33.2)	255 (31.5)	0.8225
	Non-Elective (n, %)	54 (19.7)	156 (19.3)	
	Non-Elective, Intra-partum (n, %)	129 (47.1)	398 (49.2)	
Birth weight (grams, mean $\pm$ SD)	3230 $\pm$ 490	3206 $\pm$ 477	0.0986	
5 minutes APGAR score < 7 (n, %)	11 (0.7)	13 (0.3)	0.0214	
Umbilical artery pH <7.1 (n, %)	2 (0.9)	32 (2.6)	0.1068	
NICU Admission (n, %)	57 (3.7)	212 (4.7)	0.1464	

n=number; NICU – Neonatal Intensive Care Unit; SD = standard deviation;

## SUPPLEMENTARY MATERIAL

### Definitions:

For the purpose of this study:

*Induction of labor (IOL)* 1. On admission, the woman was not in the process of active labor, had cervical dilation of 3 cm or less, and had less than three contractions during ten minutes measured by external tocometer, and 2. a medical decision of labor induction for fetal or maternal indication was documented in the obstetrical emergency room on admission or during medical follow-up. Cases of premature rupture of membranes were not considered as IOL.

*Antepartum fetal death* - if fetal death was documented prior to labor.

*Intrapartum fetal death* - if fetal death occurred during the labor process.

*Intra-uterine growth restriction* -if birthweight was below the 10th percentile. To avoid over estimation of IUGR in cases suspected for late diagnosis of stillbirth, we used the last gestational week that documented a live fetus as a reference.

*Elective Cesarean delivery* - if it was performed for maternal or neonatal indications, without evidence for compromise of either. If signs of maternal or fetal compromise were present, it was defined as a *non-elective* cesarean delivery. If the decision to perform cesarean delivery was taken during active labor, we defined the cesarean delivery as *intrapartum*.

*Maternal diabetes* - pregestational and gestational diabetes mellitus.

*Maternal hypertensive disorders* - chronic hypertension, pregnancy induced hypertension, preeclampsia, eclampsia and hemolysis, elevated liver enzymes, and a low platelet (HELLP) syndrome.