

# The effect of COVID-19 pandemic on antibiotic usage during pregnancy

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## ABSTRACT

**الأهداف:** يدرس هذا البحث استخدام المضادات الحيوية أثناء الحمل قبل وأثناء جائحة COVID-19 في مملكة البحرين.

**المنهجية:** اشتملت الدراسة على مقارنة استخدام المضادات الحيوية في مجموعتين من المرضى: المجموعة الأولى هي النساء الحوامل اللاتي ذهبن إلى مستشفى قوة دفاع البحرين في حالة مخاض نشط لمدة شهر واحد قبل جائحة COVID-19 والمجموعة الثانية تشمل جميع المرضى الذين حضروا في المخاض النشط لمدة شهر واحد خلال جائحة COVID-19.

**النتائج:** يشمل هذا التحليل 280 مريضاً دخلوا قسم الولادة قبل فترة الجائحة، و 193 مريضاً من الفترة التي تلت جائحة COVID-19. استخدم مرضى ما بعد COVID-19 المزيد من المضادات الحيوية لفترة أطول، ولوحظ الفرق الأكثر أهمية خلال الربع الثالث متبوعاً بالربع الثاني. في الربع الأول من الحمل، استخدم 4.2% من المرضى المضادات الحيوية في فترة ما بعد الجائحة مقارنة بـ 0.7% في مرضى ما قبل COVID-19. كان هناك عدد أكبر بكثير من المرضى الذين عولجوا من التهاب المهبل الجرثومي في فترة ما بعد كوفيد مقارنة بالمجموعة الأخرى.

**الخلاصة:** أكد التحليل زيادة استخدام المضادات الحيوية أثناء الحمل بعد COVID-19.

**Objectives:** To investigate the usage of antibiotic during pregnancy before and during COVID-19 pandemic in Kingdom of Bahrain.

**Methods:** This was a retrospective study of antibiotic usage in 2 groups of patients. The first group was 280 patients who attended the in active labor room pre-COVID pandemic. The second group was 193 patients who attended the labor room after the COVID-19 pandemic. Most of the data discussed below explores the impact of COVID-19 infection before the development of full vaccinations against COVID-19 in Bahrain.

**Results:** The analysis confirmed higher usage of antibiotics during pregnancy post-COVID-19 outbreak (27.9% vs [versus] 5%), and the most notable

difference was observed during the third trimester (17.1% vs 3.2%) followed by the second trimester (7.3% vs 1.1%). Likewise, there were more patients treated for urinary tract infection (16.1% vs 3.6%) and bacterial vaginosis (10.4% vs 0.7%) during the post-COVID period. There was no difference in the percentage of patients treated for upper respiratory tract infection among the groups.

**Conclusion:** The analysis confirmed higher usage of antibiotic during pregnancy post COVID19.

**Keywords:** antibiotic, pregnancy, covid-19, risk, fetal, neonatal, infant, morbidity

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Pregnancy is characterized by hormonal, immunological, and metabolic changes aimed at supporting the growth of the fetoplacental unit. Pregnancy impacts the microbiome's makeup, and the microbiome is disturbed by a single course of antibiotics.<sup>1</sup> The use of antibiotics can occasionally save lives, but they can also have unfavorable consequences, even those that are thought to be safe during pregnancy, they affect the fetus through alterations of the maternal microbiota without crossing the placenta.<sup>2</sup>

Multiple obstetrical Indications require antibiotics during pregnancy, including prevention of preterm labor in the context of premature rupture of membranes (PROM) before term.<sup>3,4</sup> Moreover, antibiotics are commonly used for the prevention of Group B *Streptococcus* neonatal disease.<sup>5,6</sup> Ampicillin combined with gentamicin is the first-line antimicrobial regimen for the treatment of clinical chorioamnionitis which should be initiated during the intrapartum period.<sup>7</sup> For the prevention of infection after cesarean section, the World Health Organization (WHO) advises giving a single dose of antibiotics 30 to 60 minutes before surgery.<sup>8</sup> One Cochrane review of 12 studies that was published in 2020 advises that one dose of antibiotics is equally effective to a longer duration of antibiotic treatment.<sup>9</sup> Regarding normal vaginal delivery, WHO guidelines 2015 recommend routine antibiotic prophylaxis for women with a third- or fourth-degree perineal tear.<sup>10,11</sup> In 2021, the WHO issued new guidelines recommending single-dose prophylactic antibiotics for women undergoing operative vaginal delivery.<sup>12</sup>

Non-obstetrics indication for antibiotics used during pregnancy including respiratory, ear, nose, and throat infections. Kidney and bladder infections are more frequent and can cause maternal organ failure.<sup>13</sup>

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the strain of coronavirus which causes coronavirus disease-19 (COVID-19).<sup>14,15</sup> Many pregnant women who are infected with SARS-CoV-2 are asymptomatic.<sup>16</sup> The main symptoms of COVID-19 in pregnancy are cough, fever, sore throat, dyspnea, myalgia, loss of sense of taste and diarrhea, moderate disease (viral pneumonia), severe pneumonia, and critical disease (acute respiratory distress syndrome), or septic.<sup>17,18</sup> Pregnant women with COVID-19 appear to be at greater risk for pregnancy complications, with more need for antibiotic use.<sup>19</sup> Fetal complications are high, including, prematurely, low birth weight, and stillbirth.<sup>20</sup>

This study is aiming to ascertain the extent of antibiotic use before and after the COVID-19 pandemic during the antenatal period and labor and its effects on birth outcomes in the Kingdom of Bahrain.

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**Methods.** This was a retrospective study, that included 2 groups of patients, first one was pre-COVID pandemic, and included all pregnant women who attended Bahrain Defense Force Hospital, Riffa, Bahrain in active labor for one month during the period between October 2019 and November 2019 (total of 280 patients). The second group was pregnant women who attended the labor room in active labor during the COVID-19 pandemic at the maximum peak of incidence in Bahrain, between May 2021 and June 2021 (a total of 193 patients recruited). Most of the data discussed below explores the impact of COVID-19 infection prior to the development of full vaccinations against COVID-19 in Bahrain. The hospital has an obstetrics and gynecology unit which runs an antenatal clinic with a resident gynecologist, pharmacist, and several midwives and nurses. The information was gathered from the operating room book, antenatal clinic data, patient medical records in the hospital, and the labor room register.

The inclusion criteria was the mother should have attended all antenatal care at the hospital after confirmation of pregnancy either by ultrasonography or human chorionic gonadotrophic detection method. Patients' characteristics such as age, body mass index (BMI), previous gravidity and parity, and past medical history are recorded. Also, labor characteristics including preterm labor, PROM, and the mood of delivery are documented. The antibiotic dose prescribed, the duration of therapy, and the frequency of administration taken into consideration are all documented in the note. All patients with partial hospital care or complete community antenatal care were excluded from the study. Furthermore, the plan was to exclude patients with confirmed COVID-19 from the second group but there were none in that month. We encountered the usage of the following individual antibiotics: amoxicillin, azithromycin, amoxicillin-potassium clavulanate, phenoxymethylpenicillin, cephalexin, clarithromycin, clindamycin, doxycycline, erythromycin, metronidazole, and nitrofurantoin. In Bahrain, antibiotics cannot be obtained without a prescription. Hence, we documented some of the most common indications for prescribing antibiotics during pregnancy before and after the COVID-19 pandemic and discuss the potential associated risks including birth weight, appearance, pulse, grimace, activity and respiration (APGAR) scores, and incidences of birth defects as indicators of birth outcomes. Poor APGAR scores included all babies born with APGAR scores less than 3 at 5 minutes. Preterm labor is defined as when regular contractions result in the opening

of the cervix between 24 and 37 gestational weeks. Premature rupture of membranes is a rupture of the membranes before labor begins, the diagnosis was based on speculum examination. The study also recorded hospital admission with and without antibiotic use and the length of hospital stay.

**Statistical analysis.** Statistical analysis was carried out using Stats Direct software (Version 3.3.5 22/03/2021 Wirral, UK). The assessment was carried out on the data to explore differences between groups with regard to basic characteristics such as age, BMI, previous pregnancies, medical history, labor characteristics, and antibiotic usage. Continuous data was analyzed using a two-sided T-test and expressed as mean±SD. Discrete variables are expressed as frequency (percentages) and calculated by the Chi-square test or Fisher's exact test. *P* values of <0.05 were considered statistically significant.

**Results.** This analysis includes a total of 473 pregnant patients who attended labor room in active labor. over the study period. A total of 280 patients were recruited prior to the pandemic, and 193 patients were recruited from the period after the COVID-19 pandemic. The basic characteristics matched regarding age, BMI, and previous parity. However, post-COVID patients were more likely to have suffered a miscarriage prior to their current pregnancy with a mean of 0.6 compared to 0.4 for patients prior to the pandemic (*p*=0.01). The groups have similar background medical histories regarding diabetes and hypertension (Table 1).

Labor characteristics assessment showed similar rates of pre-labor rupture of membrane and congenital abnormalities. Furthermore, fetal gender, birth weight, and poor APGAR score babies were all similar between the groups. Post-pandemic patients have markedly higher preterm labor at 12.4% vs 3.9% (*p*=0.0005) and lower cesarean birth at 14.5% vs 25.7% (*p*=0.004) (Table 2).

Post-COVID patients have a higher admission rate at 18% vs 8.2% (*p*=0.001). However, admission with infection was similar between the groups. Furthermore, the length of stay in the hospital did not differ between the groups. Post-COVID patients used more antibiotics and for a longer period of time at 27.9% vs 5% and mean days of 1.4 vs 0.3 in the order provided. The most significant difference in usage was noted during the third trimester at 17% vs 3.2% (*p*<0.0001) followed by the second trimester at 7.3% vs 1.1% (*p*= 0.001). In the first trimester, 4.2% of patients used antibiotics in the post-pandemic period compared to 0.7% in the pre-COVID patients (*p*=0.02). There were significant patients treated for bacterial vaginosis (BV) in the

**Table 1 -** Differences in patients' characteristics before and after the COVID-19 pandemic.

Parameters	Pre COVID n=80 (%)	Post COVID n=193 (%)	P-value
Maternal age	29.2±5.9	28.6±5.4	0.22
BMI	30.9±6.2	31.2 ±5.4	0.72
Gravida	3.5 ±2.3	3.6 ±2.1	0.65
Parity	2.2±2	2.1 ±1.7	0.62
Miscarriage	0.4 ±0.7	0.6 ±0.8	0.01
DM	37 (13.2)	27 (13.9)	0.81
PIH	7 (2.5)	3 (1.6)	0.54

BMI: body mass index kg/m<sup>2</sup>, DM: diabetes mellitus, PIH: pregnancy induced hypertension

**Table 2 -** Differences in labor characteristics before and after the COVID-19 pandemic.

Parameters	Pre COVID n=280 (%)	Post COVID n=193 (%)	P-value
PROM (%)	2 (0.7)	5 (2.6)	0.13
Preterm labor (%)	11(3.9)	24 (12.4)	0.0005
Congenital anomalies (%)	1 (0.4)	2 (1.04)	0.57
CS (%)	72 (25.7)	28 (14.5)	0.004
Gender (%)			
Female	136 (48.6)	89 (46.1)	0.59
Male	144 (51.4)	104 (53.9)	
Poor Apgar score (%)	6 (2.1)	2 (1.04)	0.48
Birth weight (kg)	3.2±0.5	3.2±0.6	0.97

PROM: premature rupture of membranes, CS: cesarean section

post-COVID period compared to the other group at 10.4% vs 0.7% (*p*<0.0001). Likewise, there were more patients treated for urinary tract infection (UTI) during the post-COVID period at 16.1% vs 3.6% (*p*<0.0001). There was no difference in the percentage of patients treated for upper respiratory tract infection (URTI) among the groups (Table 3).

**Discussion.** Considerable evidence suggests that the COVID-19 pandemic is driving up the rate of the overuse of antibiotics.<sup>21</sup> One meta-analysis estimates that antibiotic prescription for COVID-19 was 0.80 (95% CI: 0.72–0.88), whereas antibiotic use among patients with non-COVID-19 infections was 0.54 (95% CI: 0.49–0.58). In 50% of cases, antibiotics administration is inappropriate prescriptions 0.52 (95% CI: 0.32–0.72).<sup>22</sup>

This analysis was carried out to ascertain the effect of COVID-19 on the usage of antibiotics during pregnancy and labor. This study was carried out before vaccination reflecting the tangible attitude of patients and clinicians to prevent serious infection in the absence of vaccination. The first notable difference is the number of patients

**Table 3** - The effect of Covid 19 on antibiotic usage during pregnancy and labor.

Parameters	Pre Covid n= 280 (%)	Post Covid n= 193 (%)	P-value
Antenatal admission	23 (8.2)	35 (18.1)	0.001
Antenatal admission with infection	10 (3.6)	10 (5.2)	0.39
Length of hospital stay	0.13 ±0.7	0.25 ±1.4	0.27
Use of antibiotics during pregnancy	14 (5)	54 (27.9)	<0.0001
<i>Use of antibiotics per trimester</i>			
1 <sup>st</sup>	2 (0.7)	8 (4.2)	0.02
2 <sup>nd</sup>	3 (1.1)	14 (7.3)	0.001
3 <sup>rd</sup>	9 (3.2)	33 (17.1)	<0.0001
Duration of usage	0.3 ±1.3	1.4 ±2.7	<0.0001
<i>Indications</i>			
BV	2 (0.7)	20 (10.4)	<0.0001
BV/UTI	0 (0)	3 (1.6)	0.07
URTI	2 (0.7)	0 (0)	0.35
UTI	10 (3.6)	31 (16.1)	<0.0001

BV: bacterial vaginosis, UTI: urinary tract infection, URTI: upper respiratory tract infection

recruited in the 2 periods of the study. There were far fewer patients in the post-COVID-19 group as many patients will address any medical concern during the antenatal period outside the hospital setting to reduce COVID-19 exposure risk. Furthermore, post-COVID patients tend to avoid big teaching hospitals and aim for delivery at a private hospital with limited exposure to risks.

Our analysis shows that, although patients in the 2 groups have similar age, BMI, previous parity, and medical history, the post-COVID patients were more likely to have suffered a miscarriage prior to their current pregnancy. It is not clear from this analysis if the increased miscarriage is actually related to COVID-19 or just a random finding. However, there is a lot of data available on the impact of COVID-19 infection on first- and second-trimester pregnancy loss. A nationwide study in the United States of America reported no increase in the risk of fetal loss prior to 20 weeks of gestation because of COVID-19 infection.<sup>23</sup> Other studies have also confirmed similar findings, with no statistically significant increase in fetal loss prior to 20 weeks of gestation following COVID-19 infection.<sup>24</sup>

Fetuses may be exposed to SARS-CoV-2 during critical periods of fetal development. Our analysis confirmed the fact that COVID-19 infection causes no reported increase in congenital anomalies and vertical transmission is uncommon. What is unknown in our cases is whether the second group had silent COVID-19 during early pregnancy. Despite over a

million confirmed COVID-19 infections worldwide, there has been no reported increase in the incidence of congenital anomalies.<sup>25</sup>

Our study showed that post-pandemic patients have significantly higher preterm labor and lower cesarean birth. It needs to be said that our record did not confirm previous exposure to COVID-19 and cannot rule out silent infection. One study was carried out to compare symptomatic with asymptomatic COVID-19 pregnant patients. The study found that symptomatic patients were associated with an increased risk of preterm birth and cesarean delivery. The study also compared mild and severe COVID-19 infection and found severe disease was strongly associated with preterm birth and cesarean delivery.<sup>26</sup>

In a systematic review, the preterm birth rate in women with symptomatic COVID-19 appears to be 2 to 3 times higher than the background rate. The review estimated the risk of preterm birth at approximately 17%. Most of these preterm births (94%) were iatrogenic.<sup>19</sup> In the initial United Kingdom obstetric surveillance system (UKOSS) study, the median gestational age at birth was 38 weeks of gestation with a preterm birth rate of 27%. Nearly half of the preterm birth was iatrogenic for maternal compromise and 15% were induced for fetal reasons.<sup>27</sup> An updated UKOSS study confirmed that preterm birth was more likely for women with COVID-19. Approximately 19% of women with symptomatic COVID-19 and 9% of women with asymptomatic COVID-19 gave birth before 37 weeks of gestation. Compared with a historical cohort of pregnant women without SARS-CoV-2, pregnant women with symptomatic COVID-19 were more likely to give birth before 32 weeks of gestation and before 37 weeks of gestation.<sup>28</sup> Further studies from Spain and the UK have confirmed this increased risk of preterm birth with symptomatic maternal COVID-19 infection.<sup>29,30</sup>

Our results confirmed lower cesarean birth post-COVID group. This observation needs to be considered with caution as the hospital's general setting could have contributed to this finding. Patients who need to go for a cesarean section as the planned procedure would have attended a private hospital with less COVID-19 exposure risk association and avoid coming to a teaching hospital. Other studies showed maternal COVID-19 is associated with an increased rate of cesarean birth. From the initial UKOSS study, 59% of women had cesarean births; approximately half of these were due to maternal or fetal compromise. The remainder were for obstetric reasons (such as progress in labor, previous cesarean birth) or maternal request

(6%).<sup>27</sup> The updated UKOSS data confirmed this trend, with a 49% cesarean birth rate for women with symptomatic COVID-19 versus 29% for a historical control group from 2018.<sup>28</sup> All the mentioned studies looked at the effect of the COVID-19 infection on cesarean birth rather than the incidence of cesarean birth in general.

Also, an analysis of our results showed that post-COVID patients have a higher admission rate of 18% vs 8.2%. This trend could reflect the fact that the level of preventive measures and precautionary intervention is likely to be higher post-COVID period. However, reassuringly, admission with infection and length of hospital stay were similar between the groups. Understandably, post-COVID patients used more antibiotics for a longer period of time. The most significant difference in usage was noted during the third trimester followed by the second trimester. This increase in antibiotic usage in the third trimester cannot be contributed to pre-cesarean antibiotic prophylaxis as our data showed less cesarean rate post COVID-19. The risk of antibiotic exposure was highest in the last trimester due to a higher incidence of undiagnosed urinary tract infections and BV. Regarding antibiotic usage during pregnancy, one study carried out by Mesah et al<sup>31</sup> in 2017, showed that most antibiotic exposure during pregnancy was in the third trimester 79%. In fact, 42.4% of all antibiotic treatments occurred within 24 hours of delivery and about 84% of these women went through cesarean section. First-trimester exposures accounted for just 16.6%. Furthermore, 4.4% of women received antibiotics in all 3 trimesters.<sup>31</sup> Our data confirmed much lower usage of antibiotics in the first trimester even after COVID-19 infection at 4.2%.

There were significantly more patients treated for BV and urinary tract infection in the post-COVID period. This trend reflects the potential change in attitude to treat some common infections either due to patients likely to ask for help more often post-COVID infection or physicians being proactive in clearing all potential risks of infection. Surprisingly, there was no difference in the percentage of patients treated for URTI among the groups.

This analysis confirmed some changes to the use of antibiotics during pregnancy post COVID-19. However, these findings reflect practice in government hospitals and do not necessarily reflect the real changes in practice as patients tend to use private care more often post COVID-19. Other factors such as undocumented use of antibiotics during pregnancy post community care visit and other ethnical social factors can limit the significance of these findings.

In conclusion, this study confirmed the trend of increased antibiotic use in pregnant patients during the COVID-19 pandemic. Interestingly, there was no change in URTI rate during COVID-19 but UTI and BV were significantly increased.

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