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Pregnancy Outcomes in Pregnant Patients with COVID-19: A Multicenter Study

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Abstract

Introduction: Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. The presence of COVID-19 in a pregnant patient can raise concerns, as other types of coronaviruses were associated with many adverse outcomes. This study aims to study the effect of COVID-19 on pregnancy outcomes. **Methods:** A prospective cross-sectional cohort study within Central First Health Care Cluster (multicentric), Riyadh, included all pregnant women with a singleton pregnancy diagnosed as COVID-19-positive. The primary outcome is the severity of COVID during pregnancy in terms of ICU admission and mortality. The participants were divided into three groups (preterm less than 37 weeks, the term from 37 - 40 weeks, and late-term after 40 weeks. In addition, parameters included: Gestational age at diagnosis, symptoms at presentation (cough, fever), presence of congenital anomalies, IUFD, mode of delivery, presence of PPH, newborn Apgar score, cord PH, need for NICU admission, and the newborn becoming infected with COVID-19 were also measured as secondary outcomes. **Results:** One hundred pregnant, COVID-19-positive women met the inclusion criteria; the average age of participants was 31.2 years (SD ± 6.4). Asymptomatic patients represented 54% of participants. Most of the deliveries occurred at 36 weeks or less as preterm delivery. Cesarean sections represented 55% of our population. Four-term mothers (12.5%), more than 37 weeks, need ICU admission compared to 13 (25%) preterm cases diagnosed with preeclampsia. No maternal death. **Conclusion:** COVID-19 during pregnancy can increase ICU admission. A high rate of preterm labor, miscarriage, cesarean section, and newborn testing positive for COVID-19 were observed among our population. No congenital anomalies related to COVID-19 were observed.

Keywords

Pregnancy, COVID-19, Preterm Labor, Miscarriage, Saudi Arabia

1. Introduction

Chinese authorities identified a novel coronavirus at the beginning of January 2020 as an etiologic agent, which is different from other known coronaviruses, including the Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV), and also different from Other common cold viruses. This novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is responsible for the current outbreak of coronavirus disease 2019 (COVID-19), which was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 [1]. As a result, many countries started to restrict freedom of movement and travel as a protective measure, and most social, medical, and market activities were paralyzed or semi-paralyzed.

COVID-19 with pregnancy can raise many concerns, as other types of coronaviruses are associated with many adverse outcomes [2]. As a result, many health organizations have rapidly published preliminary reports and documents to diagnose and manage COVID-19 in pregnancy [3] [4]. However, pregnant patients with COVID-19 have almost been delivered by cesarean delivery, usually preterm. Unfortunately COVID-19 pandemic is spreading worldwide, and many pregnant women will be affected [5].

Pregnant women with positive COVID-19 and severe pneumonia may be negatively impacted during pregnancy, including stillbirth, fetal growth restriction, and preterm birth [6]; moreover, adverse maternal and neonatal outcomes deserve careful management considerations, including delivery timing [7].

Clinical manifestations of COVID-19, including fever, cough, fatigue, and myalgia, were reported to be similar in non-pregnant women [8]. Moreover, laboratory test results, chest computed tomography (CT) findings, and a positive reverse transcription-polymerase chain reaction (RT-PCR) also with a similar result for non-pregnant adults with COVID-19 [9]. However, some questions need to be investigated, such as susceptibility compared with other populations, if COVID-19 might cause premature rupture of membrane, premature labor, fetal distress, or other complication as a subsequent result after COVID-19, or if there should be any decision on delivery mode [10].

During pregnancy, Intrauterine transmission is one of the most severe complications of viral diseases, especially when a TORCH agent [an acronym for (T)toxoplasmosis, (O)other Agents, (R)rubella, (C)cytomegalovirus, and (H)herpes Simplex viruses, which also includes Zika virus and Ebola virus] is congenitally transmitted [11]. Maternal-fetal transmission of viral diseases (except herpes virus) is usually through the hematogenous route. The virus can enter the placenta, reach the chorionic villous tree, and transmit to fetal blood vessels to the fe-

tus. This transmission mechanism does not occur with infection of pregnant women with two other pathogenic coronaviruses, SARS-CoV and MERS-CoV, while these coronaviruses have resulted in severe maternal pneumonia and maternal deaths and early pregnancy losses [12].

This study aims to determine if COVID-19 negatively affects pregnant women regarding fetal development, mode of delivery, and congenital formation due to intrauterine transmission. Also, we aim to determine if there is a risk of adverse effects in the mothers, such as miscarriage, premature delivery, or both.

2. Objective and Aim

To study the effects of COVID-19 on pregnancy outcome and the consequent events among COVID-19-positive mothers during pregnancy, intrapartum, and after delivery. Moreover, we measure the subsequent events for the newborn of COVID-19-positive mothers.

3. Methodology

A prospective cross-sectional cohort study within the Central (first) Health Care Cluster (Multicentre), Riyadh, Saudi Arabia; including four hospitals (King Saud Medical City, King Salman Hospital, Al-Iman General Hospital, and Imam Abdulrahman Al-Faisal Hospital) with one reference laboratory within first health care cluster. The Institutional Review Board, KSMC (H1RI-21-Jun20-04), approved the study. This study was conducted from July 2020 until March 15, 2021. It included pregnant women diagnosed as COVID-19 positive and within first, second, or third trimesters at any of the hospitals under the First Health Care Cluster umbrella.

Inclusion criteria included all pregnant women with singleton pregnancies diagnosed with COVID-19 by polymerase chain reaction (PCR) within the Central First Health Care Cluster. Exclusion criteria were: non-pregnant women, patients diagnosed and treated outside the Central First Health Care Cluster, or refusing to participate in the study. In addition, all the participants provided consent to participate in the study. Recruitment of the participants who met the inclusion criteria occurred in the four centers at the same time. All the participants were unvaccinated and diagnosed while they were pregnant.

Data were collected by reviewing files (hard copies), the electronic health system, and patient interviews (direct or telephone). The primary outcome is to measure the severity of COVID during pregnancy in terms of ICU admission and mortality. Parameters related to the mothers included the patient's age, gestational age of diagnosis, symptoms at presentation (cough, fever, shortness of breath, and sore throat), comorbidities (DM, HTN, and preeclampsia), mode of delivery, presence of postpartum hemorrhage (PPH) were also measured. In addition, newborn condition at delivery (alive or dead), baby 5-min Apgar score more or less than 7, cord PH, need neonatal intensive care unit (NICU) admission, presence of congenital anomalies, intrauterine fetal death (IUFD), and if

the newborn tested positive or negative for COVID-19 by swab test. Newborns were followed for 14 days after delivery. The participants were divided into three groups based on gestational Age at COVID-19 diagnoses (preterm mothers less than 37 weeks, term mothers from 37 - 40 weeks, and late term mothers more than 40 weeks). Data were collected, cleaned, and verified in an Excel sheet, after which they were coded and analyzed using Statistical Product and Service Solutions (SPSS) (IBM SPSS Statistics for Windows, Version 26.0, Armonk, NY). Chi-square and analysis of variance (ANOVA).

4. Results

A total of 240 COVID-19 positive patients were admitted to maternity hospitals within-cluster one, and only 100 pregnant women with positive COVID-19 met the inclusion criteria; the average of their age was 31.2 years (SD ± 6.4).

The participants were divided into three groups based on their pregnancy gestational age, most of the deliveries occurred at 36 weeks or less as preterm delivery with 52%, women delivered between 37 - 40 weeks represented 32% while those delivered after 41 weeks represented 16% as shown in Table 1. Thus, although the number of deliveries showed 32 cases as term delivery, which is double the number of cases compared with late-term deliveries (16 cases) in women with positive COVID-19, preterm delivery showed an even significantly higher rate with 52 cases shown in Figure 1.

Preterm-delivering mothers have had a fever in 16 cases considered a significant increase in the number of cases compared with regular and post-term deliveries. Results showed that 32 regular delivery women and 16 cases with post-delivery women (both were 100%) were having vaginal bleeding compared with only 5 cases (9.6%) for preterm delivery, also considered significant values with ($p < 0.0001$). Miscarriage occurred only in eight mothers with preterm deliveries compared with none for regular and post-term deliveries, while 21 mothers with preterm deliveries (40.4%) had a normal vaginal delivery with a significant value ($p < 0.007$). Intrauterine fetal death was shown in only 5 deliveries with preterm deliveries, while there was Intensive Care Admission (ICU) admission with 13 cases (25%) in preterm mothers with a significant value ($p < 0.0004$); more detail is shown in Table 1.

Results showed that newborn babies (NBB) delivered with negative COVID-19 have a significant high value in live newborn compared with NBB delivered with positive COVID-19; this results reflected 5 minutes Apgar score > 7 shown in NBB delivered with negative COVID-19 have a significant ($p < 0.0001$) high value and with 62 cases (98.4%) compared with NBB delivered with positive COVID-19 (20 (87%); Results showed that equally cases were admitted to Neonatal ICU (NICU) admission; in contrast for no NICU admission that only 9 cases NBB delivered with positive COVID-19 were not admitted to NICU compared with 49 cases were not admitted to NICU with a significant change ($p < 0.00001$) as indicated with more details in Table 2.

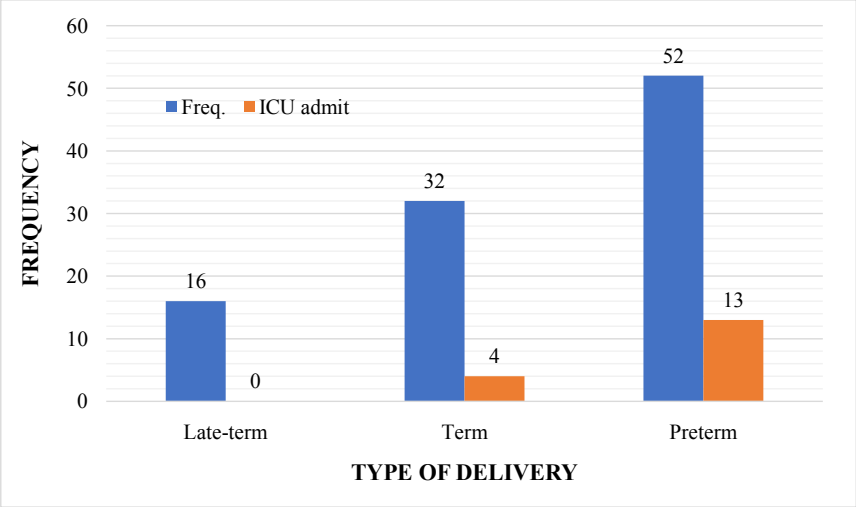

Figure 1. Frequency of type of delivery in mothers with positive COVID-19 after their deliveries according to gestational age (40 weeks and more), term delivery (37 - 39 weeks), and preterm delivery (less than 37 weeks); the figure also shows the number of patients admitted to the ICU per each group*. *Steer P. The epidemiology of preterm labour. BJOG: An International Journal of Obstetrics & Gynaecology. 2005 Mar; 112: 1-3.

Table 1. Characteristics of delivered women with positive COVID-19 according to gestational age preterm, term, and late-term deliveries.

Frequency and percentage (%)	All (n = 100)	Mothers More than 40 weeks (n = 16)	Mothers from 37 - 40 weeks (n = 32)	Mothers less than 37 weeks (n = 52)
Asymptomatic Mothers	54 (54%)	14 (87.5%)	21 (65.6%)	19 (36.5%)
Fever	24 (24%)	1 (6.3%)	7 (21.9%)	16 (30.8%)
Sore throat, Shortness of breath, Cough	26 (26%)	16 (100%)	8 (25%)	18 (34.6%)
Diarrhea	9 (9%)	2 (12.5%)	2 (6.3%)	5 (9.6%)
Vaginal bleeding	5 (5%)	16 (100%)	32 (100%)	5 (9.6%)
Other problem *	9 (9%)	16 (100%)	1 (3.1%)	8 (15.4%)
(Asthma, History of PE)**	11 (11%)	1 (6.3%)	4 (12.4%)	6 (11.5%)
Chronic diseases (DM, HTN& preeclampsia)	16 (16%)	1 (6.3%)	7 (21.9%)	9 (17.3%)
Previous uterine surgery	4 (4%)	1 (6.3%)	2 (6.3%)	1 (1.9%)
Cesarean section	55 (55%)	16 (100%)	22 (68.8%)	23 (44.2%)
Miscarriage	8 (8%)	0	0	8 (15.4%)
Normal vaginal delivery delivery	37 (37%)	6 (37.5%)	10 (31.3%)	21 (40.4%)
Postpartum Hemorrhage	4 (4%)	0	2 (6.3%)	2 (3.8%)
Intrauterine fetal death	5 (5%)	0	0	5 (9.6%)
ICU admission	17 (17%)	0	4 (12.5%)	13 (25%)

*Other problems: labor pain, vaginal leaking, or decreased fetal movement. ** PE: Pulmonary Embolism

Table 2. Characteristic of delivered newborns from mothers with a positive COVID-19 test.

Frequency and percentage	ALL	Newborns Covid Negative	Newborns Covid Positive
A live newborn	87 (100%)	63 (100%)	23 (100%)
Missing*	1 (1.1%)	0	0
5 mintues Apgar score > 7	83 (95.4%)	62 (98.4%)	20 (87%)
5 mintues Apgar score < 7	4 (4.6%)	1 (1.6%)	3 (13%)
Cord PH ≥ 7.2	75 (86.2%)	59 (93.7%)	15 (65.2%)
Cord PH ≤ 7.2	12 (13.8%)	4 (6.3%)	8 (34.8%)
NICU admission	29 (33.3%)	14 (22.2%)	14 (60.9%)
No NICU admission	58 (66.7%)	49 (77.8%)	9 (39.1%)
Weight of newborns (SD)	2.86 Kg (±0.65)	2.96 Kg (±0.56)	2.58 Kg (±0.81)

* No swab result was found in the system.

Results also showed that the asymptomatic patients represented 54% of all our participants. At the same time, the percentages of symptomatic mothers versus asymptomatic mothers are almost the same for all pregnant women according to gestational age categories. Also, the cesarean section represented 55 (55%) among our population as a mode of delivery compared with 37 (37%) with normal vaginal delivery, miscarriage (abortion) in eight cases; and 17 (17%) cases were admitted to the ICU. Four cases were due to postpartum hemorrhage, and the other 13 patients were due to severe preeclampsia. In terms of ICU admission, results showed escalating increments for the term deliveries 4 cases (12.5%) compared with late-term delivery (zero cases for ICU admission). More escalating increment showed with preterm delivery, 13 cases (25%). The ICU admission reflected the severity of COVID-19 infection. No maternal death was observed.

The eight miscarriage cases (15.4% out of 52) were all in mothers in the preterm delivery category. Seventeen mothers were admitted to the ICU, and of these, 13 had preterm labor, and four were delivered vaginally. Only four (4%) of the mothers had a postpartum hemorrhage, two women delivered vaginally, two delivered by cesarean section, and two were preterm delivery.

A total of 87 newborns were delivered alive, and the other 13 fetuses (eight missed miscarriages and five IUFD). The average weight of an alive newborn was 2.86 (±0.65 SD) kg. The comparison average weight of the COVID-19-negative newborns (n = 63, 72.4%) was 2.96 ± 0.56 SD) while newborns with COVID-19-positive (n = 23, 26.4%) were 2.58 kg (±0.81 SD), as it is illustrated in table (**Table 2**).

Seventy-five newborns had a cord pH ≥ 7.2, sixteen cases (100%) were delivered after 41 weeks, 29 cases (90.6%) were delivered vaginally, and 30 cases were delivered as preterm. On the other hand, only 12 cases (12%) had cord PH ≤ 7.2, nine were preterm delivery, and three were delivered vaginally.

The mode of delivery for the alive newborns was 54 (62.1%) delivered by cesarean section, and 33 (37.9%) newborns were normal vaginal delivery. Only four cases (4.6%) had a low 5-min Apgar scores (<7). Most newborns (75, 86.2%) were with pH ≥ 7.2, and 12 newborns (13.8%) were pH ≤ 7.2.

Two-thirds (58 cases) of the live newborns were not admitted to the NICU, and 29 newborns were admitted to the NICU due to prematurity or respiratory depression. Of these, 14 newborns tested negative for COVID-19, and 14 newborns tested positive. Interestingly, there were equal percentage distributions for preterm less than 37 weeks, term, and late-term deliveries more than 40 weeks in all alive newborns, that was applied for alive newborns with negative COVID-19 and alive newborns with positive regardless of the newborn testing positive or negative for COVID-19.

5. Discussion

Once the COVID-19 outbreak was recognized, all elective procedures were put on hold, and clinics were converted to virtual clinics. All hospitals were prepared with complete types of equipment to deal with COVID-19 positive cases. This study shows that most of our patients were diagnosed during the third trimester ≥ at 28 weeks, and most (52%) had preterm delivery less than 37 weeks and delivered newborns with an average weight of 2.86 kg. This finding is comparable to a recent metanalysis, which showed that SARS-CoV-2 infection was associated with low birth weight and preterm birth [13]. Another study found that COVID-19 mitigation measures were associated with a reduced preterm birth rate [14].

Eight patients diagnosed with COVID-19 during the first trimester had a miscarriage. The histopathology reports did not show any specific findings apart from the product of conception. One study reported no increases in the risk of spontaneous miscarriage and spontaneous preterm birth in pregnant women with COVID-19 [15].

Our study includes four fetuses diagnosed with congenital anomalies in utero, two fetuses with cardiac abnormalities, one mother previously diagnosed with cardiac anomalies, and two fetuses with pulmonary anomalies. None of these findings were relevant to the COVID-19 infection. In addition, the association between COVID-19 infection miscarriage and congenital anomalies was investigated in other studies, with none detecting a link between COVID-19 and congenital anomalies [16] [17]. More than half of the participants were delivered by cesarean section. The indication of cesarean section was obstetrics indication. Meanwhile, we can not neglect the stress of the COVID-19 crisis, which can affect the decision on the mode of delivery.

Most (54%) of the participants were asymptomatic and were swabbed when they presented to the emergency department (ED) for other obstetric complaints, as per hospital protocol. The most common presenting symptoms that brought them to ED were shortness of breath and cough (26%), followed by fev-

er (24%) and diarrhea. Our rate of asymptomatic patients is higher than reported in the literature and can vary due to seasonal, social, and clinical factors. One study showed that 30% of pregnant women were asymptomatic at the time of admission to the hospital. Cough and myalgia were the most frequent presenting symptoms [18].

Another study showed that the most common symptoms of COVID-19 in the general population are fever (91%), cough (67%), fatigue (51%), and dyspnoea (30%) [19].

For pregnant women, the most common symptoms are fever (68%) and cough (34%), with other symptoms including dyspnoea (12%), diarrhea (6%), and malaise (12%) [20].

Intrauterine fetal death occurred in 5% of our study participants during the second trimester; one was with multiple congenital anomalies. The other four death were unexplained and cannot be linked to COVID-19 infection. There were no intrapartum, or early neonatal deaths were reported. This could be explained by the fact that those cases were managed by expert midwives, obstetricians, and neonatologists. In comparison, a meta-analysis showed the perinatal death is 11.1% (5 of 60, 95% CI, 84.8e19.6), including three stillbirths and two neonatal deaths [21].

In this study, 17% of the mothers were admitted to the ICU, and 13 patients diagnosed with severe preeclampsia ,and per protocol such patients should be managed in the ICU regardless of COVID-19 status. One patient was intubated due to complications of severe preeclampsia and COVID 19; no maternal death was reported. Another study showed that 34.1% of pregnant women affected by COVID-19 infections (22 of 70) were admitted to the ICU, and 26.3% (16 of 69) needed mechanical ventilation; maternal death happened in 12.3% of all reported COVID-19 related disease cases (9 of 79) [21].

Another study showed that pregnant women with COVID-19 are at increased risk of requiring admission to an intensive care unit (ICU), ventilation, and extracorporeal membrane oxygenation (ECMO) compared to non-pregnant women. The study addresses that pregnant women with COVID-19 had an increased risk of gestational diabetes and preeclampsia than those without COVID-19 [22].

In the UK, Preterm delivery affected 47% of women hospitalized with COVID-19, and a reasonable worst-case scenario of 80% of the population being affected is realized [23].

Fifty-five mothers delivered by cesarean section; among these, 23 were preterm, and four had a previous history of uterine surgery. In addition, preterm delivery was indicated due to the mother's obstetric history or acute presentation, which indicated delivery.

Another study showed that COVID-19 infections were associated with preterm birth, stillbirth, and lower birth weight but not with the cesarean delivery rate [13].

Interestingly, 23 (26.4%) of the newborns delivered to positive COVID-19

mothers; most 20 (23%) of those mothers became infected when mothers got infected in the third trimester. These newborns were diagnosed with nasopharyngeal swab within the first week after delivery, but no placental swabs were taken. This percentage was higher than reported in other literature. The role of vertical transmission could not be excluded. In a retrospective cross-sectional study, 45 newborns were born to mothers with positive COVID-19, of which only three (6.6%) were tested positive by throat swab [24]. Another study included 836 newborns of COVID-19-positive mothers; only 35 newborns (4.2%) tested positive by polymerase chain reaction (PCR), and most of them were asymptomatic [25]; however, none of the previous studies reported in which trimester the pregnant women had tested positive.

Twenty-eight newborns (32%) were admitted to NICU; 14 newborns tested positive for COVID-19 while the other 14 were negative. Of these, 12 babies (13.8%) had a cord pH < 7. 2. The main reason for admission to NICU was prematurity, followed by respiratory depression. Our findings are comparable with another study in which 69 of 251 (27.5%) infants were admitted to the NICU [26].

Vertical transmission was not measured in this study, but there is growing evidence for vertical transmission of COVID-19 [27]. Regarding COVID-19 in pregnancy, the American College of Obstetricians and Gynecology (ACOG) recommends that pregnant individuals have access to COVID-19 vaccines [28].

With the widespread COVID-19 vaccine among pregnant women, the Saudi ministry of health (MOH) started offering it to pregnant women. Strong rising evidence showed the safety of the COVID-19 vaccine. One study shows that COVID-19 vaccination in pregnancy does not affect perinatal outcomes [29]. A systematic review and meta-analysis showed that the probability of adverse perinatal outcomes is similar between vaccinated and unvaccinated pregnant women [30].

One study showed that COVID-19 during pregnancy might be associated with preeclampsia-like syndrome, which could be diagnosed by angiogenic markers [31].

Moreover, another study found that gestational hypertension and preeclampsia might be risk factors for SARS-CoV-2 infection and its complications [32]. On the other hand, another study showed that symptomatic COVID-19 infection does not strongly increase the risk of preeclampsia during pregnancy [33].

6. Conclusion

In conclusion, the course of COVID-19 was mild and asymptomatic in most of the COVID-19-positive mothers attending the Central First Health Care Cluster. However, COVID-19 can increase ICU admission, especially if mothers with other comorbidities. COVID-19 increases rates of miscarriage, preterm labor, newborns with positive COVID-19 and cesarean section. No congenital anomalies were detected in newborns as a consequence of COVID-19 infection.

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Authors' Contribution

All authors had equal contributions to this manuscript.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviation

CT; Computed tomography
COVID-19; Coronavirus diseases 2019
ED; Emergency Department
ICU; Intensive Care Unit
IUFD; Intrauterine Fetal Death
KSMC; King Saud Medical City
(MERS-CoV); Middle East respiratory syndrome
NICU; Newborn Intensive Care Unit
PCR; Polymerase Chain Reaction
PPH; Postpartum Hemorrhage
(RT-PCR); Reverse transcription-polymerase Chain Reaction
SARS-CoV-2; Super Acute Respiratory Syndrome Coronavirus 2
SPSS; Statistical Package for the Social Sciences
ACOG; American College of Obstetricians and Gynecology
TORCH; (T)oxoplasmosis, (O)ther Agents, (R)ubella, (C)ytomegalovirus, and (H)erpes Simplex viruses
UK; United Kingdom
WHO; World Health Organization