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# MATERNAL AND PERINATAL OUTCOMES IN COVID POSITIVE WOMEN WITH GESTATIONAL DIABETES MELLITUS

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## ABSTRACT

**Introduction:** Gestational diabetes mellitus (GDM) is one of the most common medical disorders found in pregnancy. It has become a global public health burden, especially in Asians who are genetically more prone to insulin resistance. .SARS-CoV-2 infection causes respiratory distress syndrome and multisystem organ failure. Pregnant women are particularly susceptible to respiratory pathogens and severe pneumonia. Diabetes is a major risk factor for increased morbidity and mortality from COVID-19. **Objective**: To find the maternal and perinatal outcomes in terms of, cesarean section rate, prevalence of preterm delivery, live births and APGAR score in COVID positive patients with GDM. **Methods:** Prospective cohort study conducted in a tertiary care hospital. **Results:** Total 60 participants were included and divided into two groups of COVID positive (group A) and negative (group B) women with GDM. COVID positive women had more spontaneous onset of labor (80%) but caesarean delivery (53.3%) at comparatively preterm gestation (66.7%) than COVID negative women who had successful vaginal deliveries (70%) at term gestation (70%). However, live birth rate was equal in both the groups (93.3%) with APGAR score majorly 9 but nursery/NICU admission was higher in group A (56.7%). No congenital anomalies were noted in COVID group also no case of vertical transmission of infection. **Conclusion:** COVID infection in pregnant women with GDM has favourable perinatal outcome with respect to high live birth rate, no congenital anomalies, but also did increase maternal morbidity in view of high caesarean deliveries and perinatal morbidity in view of high prematurity of newborns. Multi disciplinary approach for management of both co-morbidities can prevent most of their adverse outcomes.

**KEYWORDS:** COVID, GDM, Caesarean delivery, Nursery/NICU, Preterm.

## INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance that either commences or is first diagnosed in pregnancy.[1] It is one of the most common medical disorders found in pregnancy. It has become a global public health burden, especially in Asians who are genetically more prone to insulin resistance. In India prevalence of GDM is estimated to be 10-14.3% and is expected to increase.[2]

Corona virus disease 2019 (COVID 19) is caused by severe acute respiratory syndrome corona virus 2(SARS-COV-2) and was first reported in Wuhan, Hubei province, China in December 2019.[3] It has high infectivity rate and spread is through respiratory secretions. The viral disease spread rapidly across the globe and was declared a pandemic by WHO on March 11, 2020.[4] Pregnant women are particularly susceptible to respiratory pathogens and severe pneumonia due to various factors such as physiologic changes in the immune and cardiopulmonary systems.[5] Infectious pneumonia is a significant cause of morbidity and mortality amongst pregnant women.[4] Women with GDM are at increased risk of gestational hypertension, preeclampsia, polyhydramnios, obstructed labor, uterine atony, postpartum hemorrhage and instrumental delivery or cesarean section. Adverse perinatal outcomes include risk of congenital abnormalities, stillbirth, prematurity, respiratory distress, macrosomia, neonatal hypoglycemia or hypocalcemia.[2,6] Currently there is limited information related to COVID 19 in pregnancy but members of the corona virus family such as SARS-COV and middle east respiratory syndrome (MERS-COV) are reported to be associated with severe complications during pregnancy like miscarriage, fetal growth restriction, preterm birth and maternal deaths.[7] Adequate control of blood glucose during pregnancy has been noted to reduce certain perinatal complications. However, patients diagnosed with GDM are potentially at a higher risk for a severe COVID 19 infection due to predisposing factors such as hyperglycemia, concomitant obesity and hypertension and a thorough analysis of

effect of COVID infection on pregnancy with gestational diabetes mellitus is important to ameliorate further maternal and neonatal morbidity.[8]

## MATERIAL AND METHODS

**Place of study:** Department of Obstetrics And Gynaecology, Maulana Azad Medical College and Associated Lok Nayak, G.I.P.M.E.R and G.N.E.C Hospital, New Delhi 110002.

**Study duration:** 9 months (January 2021 To September 2021)

**Study design:** Prospective cohort study.

**Study population:** Antenatal women in third trimester admitted or delivered in Lok Nayak Hospital or post natal women with post partum period < 12weeks admitted in Lok Nayak Hospital.

### Inclusion criteria

- Antenatal patients with period of gestation > 28 weeks
- Postnatal women with post partum period <12 weeks
- Diagnosed with gestational diabetes mellitus in present pregnancy
- Singleton pregnancy

### Exclusion criteria

- Pre gestational diabetes mellitus
- Known case of any chronic medical disorder like cardiac diseases, chronic hypertension or thyroid disorders.

### Outcomes

**Primary outcomes**

- Maternal outcomes
  - Gestational age at delivery
  - Mode of delivery
- Perinatal outcomes
  - Live birth/still birth(fresh/macerated)
  - APGAR score at 1 and 5 minutes

**Secondary outcomes**

- To assess maternal outcomes like gestational hypertension, preeclampsia, fetal growth restriction or preterm rupture of membranes.
- To assess fetal outcomes like weight at birth, admission to neonatal intensive care unit or respiratory distress in neonate.
- To see correlation of maternal – perinatal outcomes with COVID status of the patient in gestational diabetes mellitus.

### Sample size

To best of our knowledge, no study of COVID positive patients with gestational diabetes mellitus was available at the time of planning the study, so this **study was done as a pilot study taking 30 per group as sample size**.

### Methodology

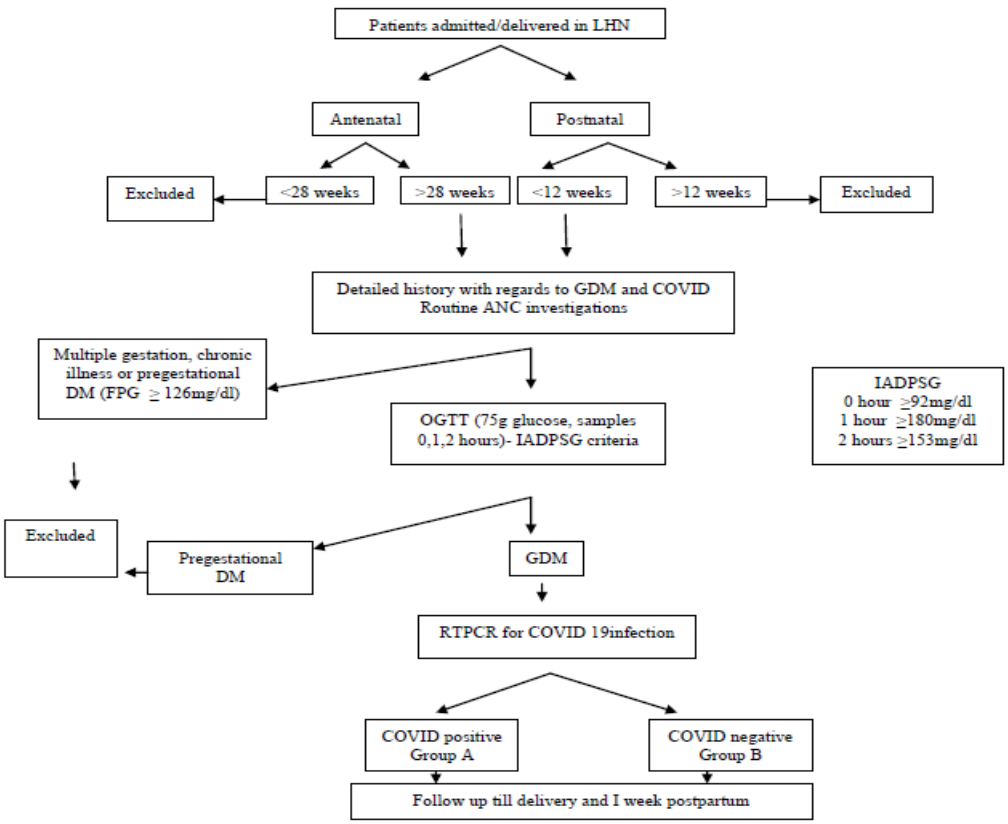


**Figure 1: Methodology.**

## RESULTS

Total of 60 participants were recruited and divided into group A (COVID positive GDM) and group B (COVID negative GDM) for comparison and statistical analysis. Both the groups are matched with respect to general characteristics like age, education, gravid, parity. Mean age of patients in group A was 29.9 ± 5.1 years and in group B was 27.6 ± 4.6 years with no significant difference between the groups. (p=0.071).Maximum patients were educated till middle class in both the groups, were multigravida and nullipara or primipara i.e. 50% nullipara and 40% primipara in group A and 40% nullipara and 33.3% primipara in groupB. Majority of patients i.e.53.3% (n=16) had admission at 32 to 37 weeks of gestation in group A while in group B maximum patients i.e. 60%(n=18)had admission after 37 weeks. there was significant difference in POG at admission in between both the groups. (p=0.023).

**Table 1: General characteristics of both groups.**

| | Group a | Group b | P-value |
|---|---|---|---|
| **Age group in yrs** | **No (%)** | **No (%)** | |
| ≤ 25 yrs | 6(20) | 10(33.3) | 0.071 |
| 26 -30 yrs | 9(30) | 13(43.3) | |
| 31 -35yrs | 12(40) | 6(20) | |
| 36 -40 yrs | 3(10) | 1(3.3) | |
| **Mean ± SD** | 29.9 ± 5.1 | 27.6 ± 4.6 | |
| **Education** | | | |
| Illiterate | 0(0) | 3(10) | 0.084 |
| Primary | 7(23.3) | 5(16.7) | |
| Middle | 16(53.3) | 18(60) | |
| High school | 7(23.3) | 2(6.7) | |
| Graduate | 0(0) | 2(6.7) | |
| **Gravid** | | | |
| 1 | 9(30) | 9(30) | 0.644 |
| 2 | 10(33.3) | 12(40) | |
| 3 | 7(23.3) | 5(16.7) | |
| 4 | 2(6.7) | 4(13.3) | |
| 5 | 1(3.3) | 0(0) | |
| ≥6 | 1(3.3) | 0(0) | |
| **Parity** | | | |
| 0 | 15(50) | 12(40) | 0.319 |
| 1 | 12(40) | 10(33.3) | |
| 2 | 3(10) | 6(20) | |
| ≥3 | 0(0) | 2(6.7) | |
| **POG at admission** | | | |
| <32 weeks | 4(13.3) | 2(6.7) | **0.023*** |
| 32-37 weeks | 16(53.3) | 7(23.3) | |
| 37-40 weeks | 10(33.3) | 18(60) | |
| >40 weeks | 0(0) | 3(10) | |

**significant difference in POG at admission*

No risk factors were observed for GDM in maximum participants in both the groups. Among the risk factors obesity, previous history of GDM and family history were most common, present in 26.6% (n=8), 13.3% (n=4) and 23.3% (n=7) respectively in group A and 23.3% (n=7), 20% (n=6) and 6.6% (n=2) respectively in group B. Most of the patients had multiple risk factors. The groups were comparable in this respect.

**Table 2: Distribution of risk factors for GDM.**

| Risk factor for GDM | Group A No. (%) | Group B No. (%) | P-value |
|---|---|---|---|
| Spontaneous abortion | 2(6.6) | 0(0) | 0.18 |
| Elderly primigravida | 1(3.3) | 0(0) | 0.347 |
| Obesity | 8(26.6) | 7(23.3) | 0.993 |
| Family history | 7(23.3) | 2(6.6) | 0.117 |
| PCOD | 4(13.3) | 2(6.6) | 0.497 |
| Previous GDM | 4(13.3) | 6(20) | 0.359 |
| Previous still birth | 2(6.6) | 2(6.6) | 0.887 |

| | | | |
|---|---|---|---|
| Previous LGA | 0(0) | 1(3.3) | 0.280 |
| None | 11(36.6) | 14(46.6) | 0.244 |

Although maximum patients i.e.50% (n=15) in group A and 83.3% (n=25) in group B had taken medical nutrition therapy for treatment of GDM, pharmacotherapy with metformin and insulin was required by significantly higher number of patients in group A than group B. (p=0.024).

**Table 3: Treatment given for GDM.**

| | | Group A No (%) | Group B No (%) | |
|---|---|---|---|---|
| Treatment for GDM | MNT | 15(50) | 25(83.3) | 0.024* |
| | MNT+metformin | 12(40) | 4(13.3) | |
| | MNT+metformin +insulin | 3(10) | 1(3.3) | |

**Significant difference with COVID positive patients requiring more metformin and insulin in addition to MNT.*

Among the study participants of group A maximum were asymptomatic that is 63.3%(n=19), 30% (n=9) were in mild category and 6.7% (n=2) in moderate category and none in severe category. Treatment for COVID comprised majorly of antibiotics given to all, only 20% of patients required additional treatment with oxygen therapy, steroids and anticoagulants like enoxaparin.

Maximum patients i.e. 80% (n=24) had delivery within 5 days of being COVID positive. Minimum interval between COVID infection and delivery was 1 day and maximum was 15 days.

**Table 4: COVID severity and treatment.**

| **Severity of COVID** | **Number(%)** |
|---|---|
| Asymptomatic | 19(63.3) |
| Mild | 9(30.0) |
| Moderate | 2(6.7) |
| Severe | 0(0) |
| **Treatment for COVID in group a** | |
| Antibiotics | 24(80) |
| Antibiotics + steroids | 1(3.3) |
| Antibiotics + steroids + oxygen +enoxaparin | 1(3.3) |
| Antibiotics + steroids +enoxaparin | 1(3.3) |
| Antibiotics +enoxaparin | 3(10) |
| **COVID positive to delivery interval** | |
| ≤5days | 24(80) |
| 6-9days | 3(10) |
| ≥10days | 3(10) |

Majority of patients in group A (n=24)80% had spontaneous onset of labor pain but had cesarean delivery (n=16,53.3%). On further subgroup analysis main indication for cesarean delivery was fetal distress.(figure2) In group B 56.7%(n=17) had spontaneous,33.3%(n=10) had induced and 10%(n= 3) had no labor pain with successful vaginal delivery in 70%(n= 21), 26.7%(n=8) cesarean delivery and only1.7%(n=1)had instrumental delivery**.** There was significant difference in onset of labor (P=0.035) but no significant difference in mode of delivery in between the groups (p0.079). In group A 66.7 (n=20) percent patients had preterm delivery with major deliveries within 32 to 37 weeks while in group B maximum patients i.e. 60%(n=18)had delivery at term within 37 to 40 weeks.(figure3) There was significant difference in POG at delivery of patients in between both the groups. (p=0.023).

**Table 5: Maternal outcomes.**

| | | **Group A N(%)** | **Group B N(%)** | P-value |
|---|---|---|---|---|
| **Onset of labour** | Spontaneous | 24(80) | 17(56.7) | 0.052 |
| | Induced | 2(6.7) | 10(33.3) | 0.009 |
| | No labor pain | 4(13.3) | 3(10) | 0.687 |
| **Mode of delivery** | | | | |
| Vaginal | | 14(46.7) | 21(70) | 0.079 |
| CS | | 16(53.3) | 8(26.7) | 0.079 |

| | | | |
|---|---|---|---|
| Instrumental | 0(0) | 1(1.7) | |
| **POG at delivery** | | | |
| Preterm | 20(66.7) | 9(30) | **<0.001*** |
| Term | 10(33.3) | 21(70) | |

**Significant difference with more preterm deliveries in COVID positive group.*

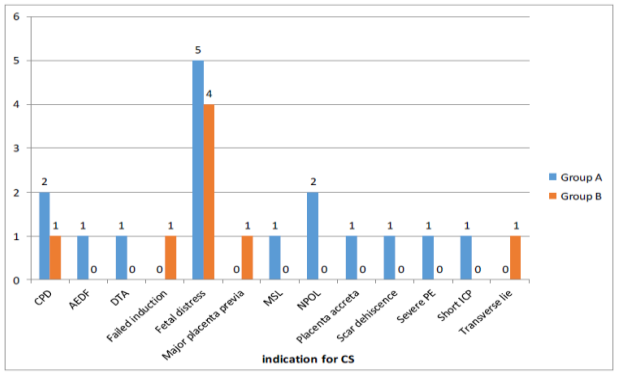


**Figure 2: Indications for CS in group A&B.**

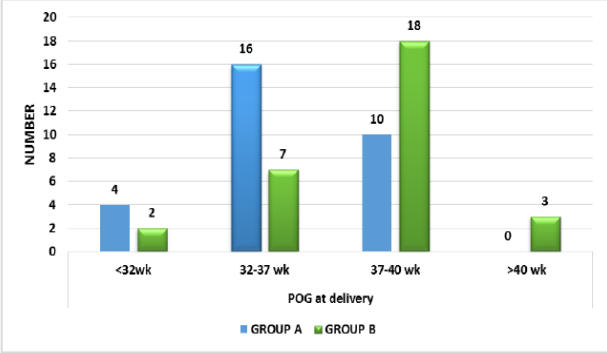


**Figure 3: Gestation at delivery in group A & B.**

Both the groups had equal number of live births and stillbirths, however nursery/ NICU admission was higher in group A. There was significant difference in nursery/NICU admission of babies in between both the groups. (p=<0.001). APGAR score at 1 and 5 minutes were comparable in both the groups being mainly 9. Majority of the neonates had birth weight between 2500 g to 3000g in both the groups i.e. 46.7% (n=14) in group A and 50% (n=15) in group B and were mostly appropriate for gestational age.(figure4) There was no significant difference in weight of babies. (p=0.949). Although, maximum babies were breastfed in both the groups i.e. 40% (n=12) in group A and 86.7% (n=26) in group B in immediate post natal period and 1 week follow up but KC feeds were also used predominantly in group B. There were no cases of vertical transmission of COVID infection.

**Table 6: Perinatal outcomes.**

| | | GroupA, N(%) | Group B N(%) | |
|---|---|---|---|---|
| **Live birth** | | **28(93.3)** | **2893.3)** | 1.000 |
| **Still birth** | | **2(6.7)** | **2(6.7)** | |
| **APGAR score At 1min** | 0-3 | 2(6.7) | 2(6.7) | 0.860 |
| | 4-6 | 1(3.3) | 0 | |
| | ≥7 | 27(90) | 28(93.3) | |
| **APGAR score At 5min** | 0-3 | 2(6.7) | 2(6.7) | 0.860 |
| | 4-6 | 0 | 0 | |
| | ≥7 | 28(93.3) | 28(93.3) | |
| **Nursery/NICU admission** | | | | |
| Yes | | 17(56.7) | 5(16.7) | **<0.001*** |
| No | | 13(43.3) | 25(83.3) | |
| **Birth weight** | | | | |
| AGA | | 21(70) | 18(60) | 0.949 |

| | | | |
|---|---|---|---|
| SGA | 8(26.7) | 9(30) | |
| LGA | 1(3.3) | 3(10) | |
| Macrosomia | 0(0) | 0(0) | |
| **Feeding status** | | | |
| Breastfeed | 12(40) | 26(86.7) | |
| Iv fluids | 2(6.7) | 0(0) | |
| Iv fluids+ RT feed | 2(6.7) | 0(0) | |
| KC + breastfeed | 3(10) | 1(3.3) | |
| KC feeds | 7(23.3) | 1(3.3) | |
| RT feeds | 2(6.7) | 0(0) | |
| Stillbirth | 2(6.7) | 2(6.7) | |

**Admission to nursery/NICU was significantly higher in COVID positive group.*

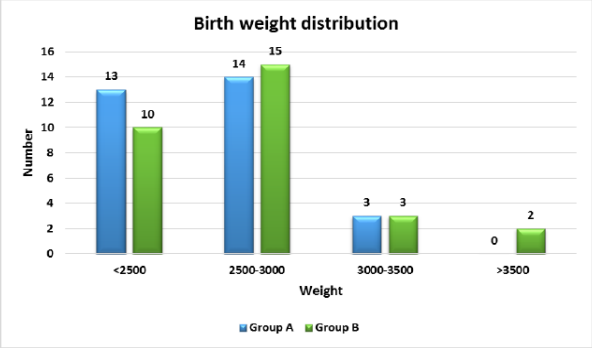


**Figure 4: Birth weight distribution in group A & B.**

**Table 7: Vertical transmission of COVID infection.**

| COVID positive **N(%)** | COVID negative **N(%)** | Not tested **N(%)** |
|---|---|---|
| 0 (0%) | 28(93.3%) | 2(6.7%) |

## DISCUSSION

Gestational diabetes mellitus represents an adverse metabolic condition to fetal development. It is associated with a high risk of fetal death. The major source of glucose in the fetus is the mother and there is a good correlation between maternal and fetal blood glucose concentrations. In pregnancies complicated by diabetes mellitus, the maternal hyperglycemia causes fetal hyperglycemia and hyperinsulinemia and analysis of blood samples obtained by cordocentesis has demonstrated significant acidemia and hyperlacticemia in the absence of hypoxemia.[9]

A systematic review of 441 cases by Gajbhiye et.al reported pregnancy complications like high cesarean section, preterm labor, fetal distress and premature rupture of membranes. The most common co morbidities with COVID 19 infection were hypertension and diabetes. Vertical transmission rate in this review was estimated to be around 8%.[10] Similarly a small, single-centre study from a London hospital showed an increase in the stillbirth rate during the pandemic (n = 16, 9.31 per 1000 births) compared with pre-pandemic(n = 4, 2.38 per 1000 births; p = 0.01). Thus, with co-existing COVID-19 infection, the adverse outcomes can worsen even more. A thorough understanding of both the conditions is essential for antenatal care and prevention of adverse obstetric outcomes.[11]

In the present study patients with coexisting COVID and GDM presented at an earlier gestation to the hospital for admission, majorly between 32 - 37 weeks similar to the meta-analysis by Dubey et.al. In 2020 of 429 articles, average gestational age at admission was 34.3 weeks.[12]

Obesity, previous history of GDM and family history are well known risk factors for GDM established from studies by Ovensen et.al.[13] obesity (71%), Prakash et.al.[14] family history (43%), and previous history of GDM (23%). Similar results were obtained in present study with no difference between COVID negative or positive group. Most common co- morbidity associated with both GDM and COVID infection is obesity being present in 26.7% (n=8) patients in group A and 30% (n=9) patients in group B.

Diabetes is one of the most relevant co-morbidity in worsening the prognosis of COVID-19. This evidence emerges particularly from the CORONADO study (corona virus sars-cov-2 and diabetes outcomes), a French nationwide multicentre observational study, aiming to identify the clinical and biological features associated with disease severity and mortality risk in people with diabetes, hospitalized for COVID-19. According to this evidence, it is clear that acute hyperglycemia has a key role as independent risk factor in COVID-19.[15] Thus, rigorous management of GDM in COVID group seemed appropriate as presented in this

study where pharmacotherapy was required more in group a.

In all studies on COVID, like by Gajhbiye et.al.[10] Li et.al.[16] Dubey et.al.[12] Juan et.al.[17] and also in present study antibiotics remain the main modality of treatment.

GDM is a risk factor for stillbirth and induction of labour is mostly opted according to glycemic control for a planned uneventful delivery. In the present study 33.3% patients with COVID negative GDM were induced showing similar induction rate in study by Bhat et.al**.** in 2012, where induction of labor was done for 58.7% GDM patients.[18] However induction rate in COVID positive patients was significantly lower (6.7%) and major women had spontaneous labour onset(80%), also, COVID positive to delivery interval was 5 days for 80% women. Thus, COVID infection may play a role in onset of labour pains. Cesarean delivery is the major mode of delivery in GDM patients and the rate further increased in coexisting COVID 19 infection as reported by Dahiya et.al.[19] (cesarean section 40%), Prakash et.al.[14] (cesarean section 44%),Antoun et.al.[7] (COVID)( cesarean section 50%),Turan et.al.[3](COVID) (cesarean section 84.1%) and present study, group A- COVID positive with GDM cesarean section 53.3%), group B- COVID negative with GDM cesarean section (26.7%). Fetal distress was the major indication of cesarean delivery similar to other studies .unlike the study by Wilk et. Al[8] present study showed significant preterm delivery rate in COVID positive women, 9.6% vs 66.7%.

Studies conducted on both GDM and COVID independently have reported favorable fetal outcomes with respect to live birth rate and APGAR score. Sreelakshmi et.al. in 2015 reported 99.5% live birth rate, Prakash et.al. in 2017 reported 100% live birth rate.[20,14] Antoun et.al. reported 100% live birth rate and Trocado et.al. also reported live birth rate of 100%.[7,4] First two studies on GDM and next two were conducted on COVID infected women. In the present study live birth rate was 93.3%(n=28) had in both the groups with 2 stillbirths and there was no significant difference in fetal outcomes in between the groups. (p=1.00). Maximum neonates had APGAR score of 9 in both groups at 1 and 5 min**.** Both stillbirths in group A were macerated stillbirth around 34 weeks period of gestation, delivered vaginally. One of them had associated gestational hypertension and the baby was small for gestational age while the other had pre eclampsia in present pregnancy and the baby was appropriate for gestational age. First patient was asymptomatic for COVID while the other was in mild category with fever as the predominant symptom. Both were taking antibiotics for treatment of COVID. For treatment of GDM, first patient maintained blood sugar control on medical nutrition therapy while the other required both medical nutrition therapy with metformin at the dose of 1 gram. Both the patients were diagnosed with hypertensive disorders after contracting COVID infection.

In group B both stillbirths were fresh stillbirths, first one at 30+6weeks and the other at 36+3 weeks. First one had associated gestational hypertension while the other had no complication. Both of the babies were small for gestational age. For treatment of GDM first patient was on medical nutrition therapy, the other was one metformin at the dose of 1.5g along with MNT. Both of the stillbirths had congenital anomalies associated like choroid plexus cyst, echogenic kidney, echogenic bowel in first and cleft lip/palate, absent right eye and absent kidney in second. Thus association with hypertensive disorders is an important risk factor for stillbirth. No congenital anomalies were reported in association with COVID infection.

Nursery/NICU admission was higher in present study as compared to other studies owing to higher preterm birth rate and thus incidence of KC feeds was also higher. In 2021, a similar study by Wilk et.al. reported 15.1% NICU admission rate in COVID positive pregnancy with GDM and 13.4% in COVID negative.[8] No vertical transmission of COVID infection was noted on testing 28 neonates by RTPCR on oropharyngeal/ nasopharyngeal sample within 24 hours of delivery. There were 2 stillbirths who were not tested. Antoun et.al. reported similar finding as the present study that all neonates were tested negative for COVID infection.[7] However, Trocado et.al. and Turan et.al in their systematic reviews have both reported 2% neonates to be tested positive for COVID 19.[4,3]

## CONCLUSION

This was a pilot study done to study the maternal-perinatal outcomes in co existing COVID infection and GDM. It was an observational study and various parameters studied were onset of labour whether spontaneous or induced, mode of delivery, gestational age at delivery and perinatal outcomes like live or stillbirth, APGAR score, birth weight, congenital malformations, nursery/NICU admissions, and neonatal complications, duration of hospital stay and various treatment received for COVID or GDM.

In the present study 80% patients had spontaneous labour in co existing COVID and GDM, and the predominant mode of delivery was by caesarean section. The caesarean section rate was as high as 53.3%. Fetal distress was the major indication for caesarean delivery and the indications for caesarean section did not differ in COVID positive women and negative women with GDM. Preterm delivery rate was also high in COVID positive women, as high as 66.7% owing to higher nursery admission. However, neonatal outcomes were favourable with 93.3% live birth rate, 90% newborns with APGAR ≥7, no congenital anomaly in babies and no case of vertical transmission of COVID infection.

Present study concludes that COVID infection in pregnant women with GDM did increase maternal morbidity in view of high caesarean deliveries and

perinatal morbidity in view of high prematurity of newborns but did not affect birth weight, stillbirth rate, APGAR score or congenital anomalies. Multi disciplinary approach for management of both co-morbidities can prevent most of their adverse outcomes.

Strength of the present study was that it was conducted in a COVID dedicated facility and most of the aspects of this infection could be studied.

Limitations of the study were that impact of severe cases of COVID infection could not be studied and some of the cases were taken retrospective.

Randomised controlled trial is needed for further research and understanding of the topic.

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