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Correspondence

Maternal and perinatal outcome in dengue and COVID-19 co-infected pregnancies



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The world is now in its fourth year of struggling with the threat of SARS-CoV-2 variants which continues to be a major public health concern. In addition, dengue is prevalent worldwide, with 50% of the world's population living in a dengue-endemic area. Of the 400 million dengue infections annually, about 40,000 die from severe dengue fever [1]. About one-third of COVID-19 or two-thirds of dengue patients are asymptomatic, but the spectrum of disease can range from mild to severe [2,3]. In immunocompromised conditions like pregnancy, the simultaneous infection with COVID-19 and dengue can be fatal not only to the affected person but also to the fetus in the mother's womb. Dengue itself has been reported to lead to maternal and fetal death as well as low birth weight and preterm delivery while COVID-19 can lead to higher rates of oxygen dependency, intensive care unit admissions, and mortality and morbidity. Although there are few reports of dengue and COVID-19 co-infection likely associated with other comorbidities, there is a lack of information and comprehensive analysis, especially in pregnant patients.

Therefore, on December 15, 2022, we conducted a detailed systematic search and analysis following PRISMA guidelines highlighting demographic, clinical, and virological factors affecting maternal and fetal outcomes of pregnant patients with dengue and SARS-CoV-2 co-infections. A total of 196 scientific publications from January 1, 2020, to December 15, 2022, with the terminologies 'dengue' or 'dengue fever' AND 'COVID-19' or 'SARS-CoV-2' AND 'pregnancy' or 'pregnant female' AND 'co-infection' or 'concurrent infection' were identified independently by two authors in five scientific databases including PubMed, EMBASE, Web of Sciences, Scopus, Research Gate and four preprint platforms for medicine and biology including MedRxiv, BioRxiv, SSRN, and F-1000R server.

After the removal of duplicate studies ($n = 32$), review articles, unavailable full texts, and articles in non-English languages, were also removed followed by 1st stage (title and abstract) and 2nd stage (irrelevant articles) ($n = 148$) screening. Of the 164 records, only 16 (9.75%) were found eligible after the 2nd stage of detailed record screening. Finally, we selected six articles; (three case reports and three retrospective studies) reporting 'dengue COVID-19 co-infections in pregnancy' with a sample size of 12 pregnant patients (Supplementary Fig. 1 and Table 1).

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A master data extraction sheet was prepared for each study including parameters such as study design, country, sample size, age of the pregnant patient, parity, gestational age (week), dengue and COVID-19 characteristics such as platelet count, and duration of hospital stay along with ICU admission, mode of delivery, obstetric complications, and maternal and fetal outcomes such as death, IUFD, and stillbirth. The majority i.e. five studies, were from Southeast Asian countries, with a maximum of three from India, and one from Canada. The mean age of co-infected pregnant patients at the time of hospitalization were 28.7 ± 5.8 years, with one patient having an advanced maternal age of 41 years. The duration of pregnancy during hospitalization ranges from 10 to 37 weeks of gestation, with the majority of the nine cases (75%) presenting above 30 weeks of gestation. Fever ranges from mild to severe and is a common symptom in all cases. Anaemia, which is a major problem in pregnant women, is reflected by mean haemoglobin of 10.4 g/dl. Thrombocytopenia which is a characteristic feature of dengue ranges from the lowest $5000/\text{mm}^3$ to $196000/\text{mm}^3$ with a mean platelet count of $20545 \pm 54596/\text{mm}^3$. Fluid management and hydration therapy are the main medications in all cases, followed by blood transfusion in four cases, of which two cases had adverse maternal and fetal outcomes, while the other two cases recovered with healthy new-borns. Concurrent dengue and SARS-CoV-2 infection in immunocompromised pregnant patients has implications for the duration of hospital stay. All 12 cases required hospitalization with a mean duration of 10.7 ± 6 days. Of the four critical cases admitted to the ICU for ventilation support, two cases had worse maternal and fetal outcomes. One mother died due to multiorgan dysfunction (MOD) with intrauterine fetal death as the neonatal outcome, while the other died of MOD and intracranial haemorrhage with stillborn. In addition, one miscarriage and one intrauterine fetal death were reported in two other admissions outside the ICU. Thus, a total of two maternal (16.7%) and four fetal (33%) deaths were attributable to mortality associated with this co-infection.

We were not able to perform a meta-analysis, due to the limited number of co-infected pregnant cases ($n = 12$), however, this is an updated systematic review that highlights the importance of co-infection in pregnancy. Further, symptomatic similarities, overlapping signs, and false positivity make earlier diagnoses difficult and misleading. Such co-infection in pregnant patients with severe

Table 1

Clinical, diagnostic characteristics, and management of included studies with Dengue COVID-19 co-infection in pregnant cases.

Study ID, Reference	Type of Study	Country	Sample size	Age	Clinical Presentation	Diagnosis of Dengue and COVID-19	Hospital stay and ICU	Medication and treatment	Maternal and Fetal outcome
Mahajan NN et al., 2020 [4]	Case Report	India	One	22	Primigravida, 37th week of gestational age, mild fever for 4 days, no petechiae, no bleeding tendencies, Hb: 12.7 g/dl; TLC:16800–12000, platelet count: 197000–343000/mm ³	Dengue NS1 Ag positive COVID-19 RT-PCR positive	9 days, No ICU admission	Antibiotics, hydration therapy, no blood transfusion	Mother: vaginal delivery through labor augmentation. Baby: PROMx2 days, IUGR fetus/ low birth weight (2.2 kg)
Irwindia R et al., 2021 [5]	Case Report	Indonesia	One	23	31 weeks of pregnancy, diagnosed as dengue shock syndrome with grade III dengue fever, multi-organ failure, Gravida 1 with 32 weeks of gestational age, Thrombocytopenia 17000/mm ³ ; IL-6: 18,812 pg/mL; IL-10: 1455 pg/mL; TNF- α : 18.11 pg/mL; IFN- γ : 5.5 pg/mL Platelets: 94000/mm ³	Dengue NS1 Ag and IgM positive COVID-19 RT-PCR positive in NPS	5 days, including ICU admission for ventilation	Thrombocyte concentrate two packs	Mother: death due to multiorgan dysfunction failure Foetus: intrauterine fetal death (IUFD)
Schulte HL et al., 2021 [6]	Retrospective study	Brazil	Two	–	Retro-orbital pain, arthralgia, myalgia	Dengue IgM positive, COVID-19 RT-PCR positive	Yes, Two hospitalization	Clinical improvement in 13 days. Hydroxychloroquine, Chloroquine, Enoxaparin, Azithromycin, Ceftriaxone	Mother: gave birth without any complications
				–	Pregnancy gestational diabetes, chronic gastritis depression, platelets:196000/mm ³ , Fever, dry cough, myalgia, sore throat, nasal congestion, diarrhoea, anosmia, ageusia, and pruritus	Dengue IgM positive, COVID-19 RT-PCR positive	Yes, No ICU	Analgesics, prednisone, hydration with 0.9% saline	No pregnancy-related complications until 10th week of pregnancy
Wijesinghe V et al., 2022 [7]	Retrospective study	Sri Lanka	Four	24	33 weeks of gestation, immune thrombocytopenic purpura (ITP) remission, Third pregnancy, fever, arthralgia, shortness of breath, sore throat; Platelets: 8000/mm ³ on day 13, progress to critical dengue haemorrhagic fever (DHF), USG showed bilateral pleural effusions	Dengue NS1 Ag positive COVID-19 RT-PCR positive SARS-CoV-2 Abs' positive (13th day)	17 days, including 5 days in ICU during the leaking phase	Anti-coagulated with subcutaneous enoxaparin (40 mg). Oral prednisolone (20 mg), IV hydrocortisone (100 mg), transfused 250 cc of RCC	Mother: survived with elective caesarean section at 37 weeks. Baby: delivered with 2.6 kg birth weight.
				31	30 weeks gestation, presented with per-vaginal bleeding at 8 weeks of period of amenorrhea (POA), 6th pregnancy, platelets:101000/mm ³ . Temp.:100°F,	Dengue NS1 Ag positive COVID-19 RT-PCR positive	10 days, No ICU	–	Mother: had miscarriage, but survived and discharged without other complications
				41	Advanced maternal age with multiple comorbidities, admitted at 30th weeks of gestation, 2nd pregnancy, Diabetes	Dengue NS1 Ag positive (20th day of admission) COVID-19	24 days, including ICU admission for ventilation support	IV ceftriaxone (1 g), oral clarithromycin (500 mg), oral dexamethasone (2 g), subcutaneous	Mother: elective caesarean section at 37th week, discharged after 11th day of post-partum Baby: delivered with

(continued on next page)

Table 1 (continued)

Study ID, Reference	Type of Study	Country	Sample size	Age	Clinical Presentation	Diagnosis of Dengue and COVID-19	Hospital stay and ICU	Medication and treatment	Maternal and Fetal outcome
					mellitus II, nephropathy, retinopathy, chronic hypertension, Platelets: 109000/mm ³ , Hb:9g/dl, chest x-ray showed bilateral patchy infiltrates, 94% air saturation	RT-PCR positive		enoxaparin (40 mg); 3 units of RCC transfused	jaundice and 2.9 kg body weight
				32	1st pregnancy with fever, arthralgia, myalgia, 28 weeks of gestation, Hb:11 g/dl; platelet: 213000/mm ³ , reduced fetal movement on 7th day of illness, admitted on 8th day with platelet: 74000/mm ³	Dengue IgM positive, Dengue NS1 Ag and IgG negative SARS-CoV-2 rapid Ag positive	Admitted on 8th day, No ICU	Fluid management	Mother: recovered without complications Fetus: Intrauterine fetal death (fetal weight 1.1 kg)
Ravindra P et al., 2022 [8]	Case report	India	One	29	33 weeks gestation, fever (4 days duration), cough, Platelet: 68000/mm ³ , 4 days of fever, no rash and no dyspnea, Hb: 11.6 g/dL; TLC: 2800/mm ³ ; CRP: 12.43 mg/L; COVID-19 unvaccinated individuals, the severity of COVID-19 is mild	Dengue NS1 Ag positive COVID-19 RT-PCR positive	7 days stay, No ICU	Oral fluids and antipyretics.No steroids, anticoagulants, or no platelets transfusion is required	Mother: uneventful recovery and discharged
Agarwal V et al., 2022 [9]	Retrospective study	India	Three	22	Primipara, Parity: P1L0; 36 week gestation; admitted with post-partum haemorrhage (PPH) in shock on post-natal day 0, platelets: 18000/mm ³ , Hb:10.9 g/dl; TLC 61,000 µl; Fever: 98°F; elevated AST/ALT:7241/1989 and total bilirubin of 6.1 g/dl	Dengue NS1 Ag positive COVID-19 RT-PCR positive	14 days including ICU admission	Supportive management with antibiotics, invasive mechanical ventilation (due to ARDS), hydration with multiple blood transfusions	Mother: spontaneous VD at 36th week and death due to MOD, intracranial hemorrhage, and HE on post-natal day 14 Baby: delivered a stillborn baby of 2.4 kg
				34	Multiparous, Parity: G3P2L1; 37th week of gestation, high-grade fever:101°F, petechial rashes, with total bilirubin:22 g/dl Hb 8.3 g/dl; TLC = 4310 µl, platelets:5000/mm ³	Dengue NS1 Ag and IgM Ab; COVID-19 RT PCR positive	6 days	Intravenous immunoglobulin, antibiotics, hydration with multiple blood transfusions. No mechanical ventilation or steroids required	Mother: spontaneous labor and VD with post-partum hemorrhage (PPH), stable on post-natal day 6 Baby: born with 3 kg body weight and tested negative for dengue Abs
				29	Multiparous, Parity: G3P2L1 with 36 week gestation period; fever:102°F, Hb:9.9 g/dl; TLC:7800 µl, platelets:86000/mm ³ , chest X-ray showed left pleural effusion	Dengue NS1 Ag; COVID-19 RT PCR positive	5 days	Hydration and antibiotics along with supportive care.No blood transfusion, steroids, IVIG, or mechanical ventilation required	Mother: vaginal delivery at 37th week, stable on post-natal day 5 Baby: delivered with 2.2 kg body weight and tested negative for dengue Abs

PROM: Premature rupture of membrane; IUGR: Intrauterine fetal growth restriction; IUFD: Intrauterine fetal death; VD: Vaginal delivery; PPH: Post-partum haemorrhage; IVIG: Intravenous immunoglobulin; ARDS: Acute respiratory distress syndrome; RCC: Red cell concentrates.

thrombocytopenia needs ICU admission for ventilation support. Maternal and fetal complications such as miscarriage, intrauterine fetal death, and stillbirth are the consequences that need to be addressed by a timely diagnosis of co-infections and comorbidities and providing appropriate medical interventions for better outcomes in

immunocompromised pregnant patients.

Author's contribution

PT, VT, and SS conceived the idea. PT and VT researched the data

and findings. PT, VT, and SS formulated the original draft of the manuscript. VT, PT, and SS reviewed and edited the draft. VT completed the corrected draft. All authors read the article and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejogrb.2023.02.017>.

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Pryanka Thakur^{a,1}, Vikram Thakur^{a,*1}, Sonakshi Srivastava^b

^a Department of Virology, Post Graduate Institute of Medical Education and Research, (PGIMER) Sector-12, 160012 Chandigarh, India

^b Department of Microbiology, All India Institute of Medical Sciences (AIIMS), Kalyani 741245, West Bengal, India

* Corresponding author.

E-mail address: vik5atif@gmail.com (V. Thakur).

¹ Authors contributed equally to this work as the shared first authors.