First trimester COVID-19 and the risk of major congenital malformations—International Registry of Coronavirus Exposure in Pregnancy

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Abstract
There is limited information about the effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during the first trimester of pregnancy on the risk of major congenital malformations (MCMs). The International Registry of Coronavirus Exposure in Pregnancy (IRCEP) was designed to estimate the relative risk of adverse perinatal outcomes among women with Coronavirus Disease 2019 (COVID-19) at specific times during gestation. Adult women were eligible to enroll if they had a SARS-CoV-2 test, regardless of the results, or clinically confirmed COVID-19 during pregnancy. Self-administered questionnaires collected data on SARS-CoV-2 infection, pregnancy outcomes (including detailed questions on MCMs), and potential confounders. The analysis of MCMs includes women with either a positive SARS-CoV-2 PCR test or a clinical diagnosis of COVID-19 during the first trimester (exposed group) or a negative SARS-CoV-2 test (reference) that enrolled while pregnant. Sensitivity analyses were restricted to participants who enrolled before the availability of informative prenatal screening tests and extended to those enrolled after end of pregnancy. Generalized linear models were used to estimate relative risks (RR) and 95% confidence intervals (CI). Of 17,163 participants enrolled between June 2020 and July 2021, 1,675 enrolled during pregnancy. Restriction to participants with complete follow-up reduced the sample size to 92 exposed and 292 unexposed reference pregnancies. MCMs were reported in 3 (3.3%) exposed and 8 (2.7%) unexposed (RR 1.2; 95% CI 0.32–4.2) newborns. The RR was 2.5 (95%CI 0.23–27) among those enrolled before prenatal screening, and 2.2 (95%CI 0.89–5.3) in the overall study population including those enrolled post-pregnancy. No specific pattern of malformations was observed. Although results are compatible with no major teratogenic effects associated with maternal SARS-CoV-2 infection, RR estimates were imprecise and larger studies are warranted.
1 | BACKGROUND

Transplacental transmission of SARS-CoV-2 and possible induction of MCMs are serious concerns for pregnant women with COVID-19. Cases of vertical transmission of SARS-CoV-2 have been described in pregnant women with confirmed COVID-19, including after first-trimester maternal infection; however, this appears to be rare (Chen et al., 2020; Breslin et al., 2020; Fan et al., 2021; Dong et al., 2020; Zeng et al., 2020; Shende et al., 2021; Valdespino-Vazquez et al., 2021). Moreover, MCMs may occur even in the absence of transplacental transmission. For example, vertical transmission of influenza virus is believed to be rare, but maternal influenza infection during pregnancy has been associated with an increased risk of neural tube defects in the infant, possibly related to maternal hyperthermia (Luteijn et al., 2014). Other maternal infections associated with MCMs include cytomegalovirus, herpes simplex and varicella-zoster virus, toxoplasmosis gondii, and Zika virus (Centers for Disease Control and Prevention, 2005; Marquez et al., 2011; Maldonado & Read, 2017; Oliveira Melo et al., 2016; Butler, 2016; Zhang et al., 2015; Stagno & Whitley, 1985). Although there is no prior evidence to support that coronaviruses impact fetal development, SARS-CoV-2 infections are new to humans and, therefore, lack of evidence is not evidence of safety.

Evaluation of teratogenicity is challenged by the need for a sufficient number of exposed pregnancies, attention to the timing of both infection and enrollment during pregnancy, and an appropriately selected reference group. In a large surveillance study that considered maternal SARS-CoV-2 infections at any time during pregnancy, 0.6% of prenatally exposed liveborns had an MCM, a low birth prevalence that likely reflects underascertainment (Woodworth et al., 2020). In a cohort study, the risk of MCMs was similar on second-trimester ultrasound scans among 80 pregnant women who tested positive for SARS-CoV-2 in the first trimester (3.8%) and in 460 pregnant women who tested negative (3.5%) (Crovetto et al., 2021). Much is still unknown about the risk of specific MCMs when COVID-19 occurs in the first trimester.

A dearth of information early in the COVID-19 pandemic led to increased levels of anxiety among pregnant women (Sinaci et al., 2020), as well as unnecessary cesarean deliveries (Chen et al., 2020) and elective pregnancy terminations (Wu et al., 2020). Therefore, there has been an urgent need to gather information. We used the direct-to-participant International Registry of Coronavirus Exposure in Pregnancy (IRCEP) to assess the relative risk of major structural congenital malformations in pregnancies exposed to SARS-CoV-2 during the first trimester (Hernandez-Diaz et al., 2022).

2 | METHODS

2.1 | Study design

The IRCEP was an international observational cohort study that enrolled participants from June 2020 until July 20, 2021. The source population consisted of pregnant or recently pregnant women 18 years of age or older tested for SARS-CoV-2 (regardless of the result) or with a clinical diagnosis of COVID-19 between the last menstrual period (LMP) and end of pregnancy. Women self-enrolled while still pregnant or within 180 days after the end of pregnancy using the IRCEP website. Every study participant provided consent electronically. Status of pregnancy (spontaneous abortion [SAB], termination, stillbirth, livebirth) was collected and livebirths were followed until 3 months after birth to capture perinatal outcomes. Follow-up started at enrollment and continued until pregnancy loss, loss to follow-up, or 90 days after delivery, since some malformations are only clinically apparent and diagnosed after birth. The IRCEP study protocol was approved by the Harvard Longwood Campus Institutional Review Board (IRB20-0622).

2.2 | Data collection

Data were collected via self-administered online questionnaires available in 10 languages. At enrollment, women completed modules on baseline characteristics (e.g., demographics, illnesses, reproductive history, prenatal screening, and its results); and on timing of SARS-CoV-2 testing and COVID-19 clinical signs, their duration, severity, and treatment. For women enrolling during pregnancy, monthly follow-up questionnaires continued until delivery, when information on obstetric and neonatal outcomes was collected. In case of early pregnancy loss, the participant was directed to a brief
End-of-Pregnancy questionnaire which inquired about malformations and subsequently ended their participation in the study. Finally, at around 90 days after delivery, a module collected information on postpartum and neonatal outcomes, with questions targeted toward malformations. Women enrolling post-delivery were able to complete all modules at enrollment.

### 2.3 Study population

The primary study population was restricted to women that enrolled before the end of pregnancy, when most malformations are typically diagnosed. However, we conducted sensitivity analyses to explore the robustness of results to selection biases derived from inclusion criteria: First, we restricted the population to women that enrolled before malformations can be detected through prenatal screening tests, that is, before 12 to 15 weeks of gestation (optimal sample). Second, we expanded the study population to include pregnancies that enrolled after pregnancy to increase numbers and precision (overall study population).

### 2.4 SARS-CoV-2 and COVID-19

Women with a positive reverse transcription-polymerase chain reaction (PCR) for SARS-CoV-2 or clinically diagnosed COVID-19 during the first 12 weeks of gestation were classified as infected. The rationale for including cases without a positive test is that in many areas of the world, early in the pandemic, PCR testing was inaccessible to a large proportion of the population and epidemiological considerations and clinical symptoms (i.e., pneumonia, chest CT findings) were considered sufficient for a positive diagnosis. The reference group includes women with a negative SARS-CoV-2 test (PCR or serologic) and no COVID-19 diagnosis during pregnancy. This group can provide an estimate of the expected incidence of MCMs in the same source population.

### 2.5 Outcome definitions

In this study, the outcome of interest was any MCM, defined as a structural abnormality with surgical,
| Characteristics                  | Enrolled before screening (optimal analysis) | Enrolled during pregnancy (primary analysis) | Enrolled during or after pregnancy (overall analysis) |
|----------------------------------|---------------------------------------------|---------------------------------------------|-------------------------------------------------------|
|                                  | Tested negative N = 1,009                    | First-trimester SARS-CoV-2 positive N = 1,072 | Tested negative N = 10,235 First-trimester SARS-CoV-2 positive N = 1,727 |
|                                  | n (%)                                       | n (%)                                       | n (%)                                                  |
| Agea                            | 29.7 (5.1)                                  | 30.7 (4.9)                                  | 30.5 (5.0)                                            |
| Education                        |                                             |                                             |                                                       |
| Less than high school            | 43 (5.5%)                                   | 118 (3.7%)                                  | 356 (4.3%)                                            |
| High school                      | 234 (30%)                                   | 808 (25%)                                   | 2,371 (29%)                                           |
| College                          | 240 (31%)                                   | 1,125 (35%)                                 | 3,065 (37%)                                           |
| Graduate education               | 266 (34%)                                   | 1,173 (36%)                                 | 2,512 (30%)                                           |
| Race/ethnicity                   |                                             |                                             |                                                       |
| Asian                            | 34 (4.3%)                                   | 181 (5.6%)                                  | 456 (5.5%)                                            |
| Black                            | 42 (5.3%)                                   | 153 (4.7%)                                  | 335 (4.0%)                                            |
| Latina                           | 126 (16%)                                   | 486 (15%)                                   | 1,207 (14%)                                           |
| Mixed                            | 81 (10%)                                    | 290 (8.9%)                                  | 690 (8.3%)                                            |
| White                            | 506 (64%)                                   | 2,133 (66%)                                 | 5,651 (68%)                                           |
| Economic status                  |                                             |                                             |                                                       |
| Poor                             | 124 (16%)                                   | 368 (12%)                                   | 928 (11%)                                             |
| Lower-middle class               | 174 (22%)                                   | 716 (23%)                                   | 1,974 (24%)                                           |
| Middle class                     | 344 (44%)                                   | 1,500 (47%)                                 | 3,839 (47%)                                           |
| Wealthy                          | 133 (17%)                                   | 583 (18%)                                   | 1,401 (17%)                                           |
| Primiparous                      | 308 (41%)                                   | 1,312 (43%)                                 | 3,585 (46%)                                           |
| Pre-pregnancy BMIa (category)    | 26.8 (6.6)                                  | 27 (7.0)                                    | 27 (7.0)                                              |
| <25                              | 326 (48%)                                   | 1,389 (50%)                                 | 3,353 (47%)                                           |
| 25–30                            | 181 (27%)                                   | 698 (25%)                                   | 1,868 (26%)                                           |
| ≥30                              | 171 (25%)                                   | 671 (24%)                                   | 1,915 (27%)                                           |
| Smoking                          |                                             |                                             |                                                       |
| Never                            | 489 (65%)                                   | 2,052 (68%)                                 | 5,312 (68%)                                           |
| Prior to pregnancy only          | 188 (25%)                                   | 720 (24%)                                   | 1,818 (23%)                                           |
| During this pregnancy            | 74 (9.9%)                                   | 245 (8.1%)                                  | 658 (8.4%)                                            |
| Pre-existing condition           | 134 (18%)                                   | 493 (16%)                                   | 1,195 (15%)                                           |
| Continent                        |                                             |                                             |                                                       |
| Africa                           | 48 (4.8%)                                   | 159 (3.8%)                                  | 441 (4.3%)                                            |
| Asia                             | 46 (4.6%)                                   | 260 (6.2%)                                  | 627 (6.1%)                                            |
| Europe                           | 357 (35%)                                   | 1,452 (35%)                                 | 3,558 (35%)                                           |
| North America                    | 310 (31%)                                   | 1,407 (34%)                                 | 3,987 (39%)                                           |
| South America                    | 247 (25%)                                   | 892 (21%)                                   | 1,616 (16%)                                           |
| Oceania                          | 1 (<0.1%)                                   | 1 (<0.1%)                                   | 1 (<0.1%)                                             |

Note: This table includes participants lost to follow-up, that is, who did not report birth outcomes and from whom we could not determine presence of a major malformation.

aMean (SD).
medical, or cosmetic importance (Holmes, 1999). MCMs were included regardless of whether they were identified prenatally or postnatally, and whether they resulted in a livebirth, SAB, or termination of pregnancy. Chromosomal or Mendelian-inherited anomalies were excluded under the assumption that the etiologies of these malformations are not attributable to infections post-conception. We did not include minor anomalies (e.g., tongue tie) or diagnoses expected in preterm newborns (e.g., patent foramen ovale). Birth defects were classified following the recommendations of the CDC National Birth Defects Prevention Study (Rasmussen et al., 2003). We focused on overall MCMs as the primary outcome since the sample size was too small to evaluate specific defects. However, we present the frequency of specific MCMs by exposure group.

2.6 Analyses

Participants who were lost to follow-up or had not provided information on the presence of malformations were excluded from the analyses. We compared the risk of MCMs between pregnancies with SARS-CoV-2 infections in the first trimester and those with a negative SARS-CoV-2 test at any time during pregnancy and no positive test or clinical COVID-19 diagnosis. Generalized linear models were used to estimate relative risks (RRs) and 95% confidence intervals (CI) (Messinger et al., 2021).

3 RESULTS

By the end of the study, 17,163 participants had enrolled from 78 countries. Among them, 1,727 had SARS-CoV-2 infection before 12 weeks of pregnancy and 10,235 had tested negative; 1,675 and 4,172 of them enrolled before end of pregnancy and 1,072 and 1,009 of them enrolled before prenatal screening for malformations, respectively. (Figure 1). Among participants enrolled during pregnancy, approximately 95% were classified as lost to follow-up. Baseline characteristics were neither substantially different between groups (Table 1) nor meaningfully associated with losses to follow-up (Table S1).

In the primary analysis, which includes only those enrolled before the end of pregnancy, the frequency of malformations was 3.3% (n = 3) in 92 participants with SARS-CoV-2 infection during the first trimester and 2.7% (n = 8) among 292 with negative tests (RR 1.2; 95%CI 0.32–4.4). (Table 2). When the sample was restricted to those enrolled before prenatal testing, the frequency of MCMs was 3.0% (n = 2) among the 66 participants exposed and 1.2% (n = 1) among the 82 with negative tests (RR 2.5; 95%CI 0.23–27). When the sample was expanded to include those enrolled after pregnancy, the risk of MCMs was 4.4% (n = 5) in 130 participants exposed and 1.8% (n = 72) among 4,049 with negative tests (RR 2.2; 95%CI 0.89–5.3). Table 3 presents the list of malformations in the expanded group. No specific pattern of MCMs was identified.

Restriction of the exposed group to those with positive PCR tests or those with symptomatic COVID-19 did not change the results. Given the small numbers, we did not conduct further analyses.

4 DISCUSSION

In this international cohort of pregnancies exposed to SARS-CoV-2 in the first trimester, the risk of any MCM

| Table 2 | Crude risks and risk ratios of major malformations among IRCEP participants with sufficient pregnancy outcome data to determine the presence of a major malformation. Data are stratified by timing of enrollment relative to end of pregnancy and prenatal informative screening for malformations (i.e., after 15 weeks gestation) |
|---------|-------------------------------------------------|-----------------------------------------------------------------|------------------|
|         | First-trimester SARS-CoV-2 | Reference (negative test) | Risk Ratio       |
|         | N Malformations (%) | N Malformations (%) | (95% CI) |
| Primary analysis (enrolled during pregnancy) | 92 3 (3.3%) | 292 8 (2.7%) | 1.2 (0.32, 4.4) |
| Sensitivity analyses—different samples | | | |
| Optimal analysis (enrolled before screening) | 66 2 (3.0%) | 82 1 (1.2%) | 2.5 (0.23, 27) |
| Overall analysis (enrolled before or after pregnancy) | 130 5 (4.4%) | 4,049 72 (1.8%) | 2.2 (0.89, 5.3) |
| Sensitivity analyses within overall sample | | | |
| Symptomatic COVID-19 | 116 5 (4.3%) | 4,049 72 (1.8%) | 2.4 (1.0, 5.9) |
| Restriction to confirmed PCR | 86 3 (3.5%) | 4,049 72 (1.8%) | 1.8 (0.59, 5.7) |

Note: SARS-CoV-2 positive cases are those with first-trimester positive PCR tests or COVID-19 symptom onset in the first trimester with clinical diagnosis and/or serology testing.
**TABLE 3** Specific malformations reported by participants with SARS-CoV-2 infection during the first trimester or with a negative test during pregnancy (reference group). The table includes malformations included in the overall analysis (i.e., from participants enrolled before or after pregnancy).

| Tested negative $n = 72$ | SARS-CoV-2 infection during first trimester $n = 5$ |
|--------------------------|-----------------------------------------------|
| **brain/nervous system** | Agenesis of corpus callosum                    |
|                          | Chiari malformation, spina bifida              |
|                          | Cyst in brain                                  |
|                          | Hydrocephalus                                  |
|                          | Hydrocephalus, ventriculomegaly                |
|                          | Microcephaly                                   |
| **Ear, face, and neck**  | Ear malformation                               |
|                          | Duodenal atresia, hearing loss/deafness*       |
|                          | Oral cleft                                     |
| **Cardiac and circulatory system** | Aortic valve stenosis                        | Cardiac malformation (x2) |
|                          | Aortic valve stenosis, bicuspid aortic valve (×2) |
|                          | Atrial septal defect (×3)                      |
|                          | Atrial septal defect, cardiac hypertrophy      |
|                          | Atrial septal defect, pulmonary valve atresia or stenosis |
|                          | Cardiac malformation (×2)                     |
|                          | Cardiomyopathy                                 |
|                          | Coarctation of aorta (×3)                     |
|                          | Congenital heart disease that required hospitalization |
|                          | Hypoplastic right heart                        |
|                          | Patent foramen ovale, arteriovenous malformation |
|                          | Patent foramen ovale, cyst (surgery required to remove cyst) |
|                          | Patent foramen ovale, horseshoe kidney*       |
|                          | Pulmonary valve atresia or stenosis           |
|                          | Tetralogy of Fallot (×2)                      |
|                          | Tricuspid insufficiency                        |
|                          | Ventricular septal defect (×3)                |
|                          | Ventricular septal defect, atrial and ventricular malformation |
| **Respiratory**          | Congenital cystic adenomatoid malformation, pulmonary airway malformation in ultrasound |
|                          | Congenital pulmonary airway malformation       |
| **Digestive system**     | Biliary tract anomaly                          |
|                          | Duodenal atresia, hearing loss/deafness*       |
|                          | Esophageal atresia                             |
|                          | Pyloric stenosis (×2)                         |
| **Genital**              | Cryptorchidism (in term infant requiring surgery) |
|                          | Hypospadias (×2)                              | (Continues)
did not differ significantly from that reported by an internal reference group with negative SARS-CoV-2 tests. However, outcome data were available on only 92 pregnancies for the primary analysis because more than 95% were lost to follow-up. No specific pattern of malformations was identified among the 3 children with congenital anomalies reported after first trimester maternal SARS-CoV-2 infection. This is reassuring since most teratogenic exposures identified in the past have been associated with a specific pattern of MCMs (e.g., congenital cytomegalo-virus, rubella, thalidomide) (Centers for Disease C, Prevention, 2005; Newman, 1985; Messinger et al., 2020).

Our study enrolled a large international cohort of pregnancies, included an internal reference group and focused on infections during the first trimester, that is, the presumed etiologically relevant period for embryogenesis. Moreover, we restricted the primary analysis to participants prospectively enrolled before the end of pregnancy, when most malformations are identified, and sensitivity analyses further restricted the study population to those enrolled before prenatal screening. Enrollment after pregnancy outcomes are known may self-select a group with adverse outcomes, who are more eager to share their experience in a study, thus overestimating risks; or it might underestimate the risk if the distressing event reduces the likelihood of participation (Margulis et al., 2015). If participation after an adverse outcome is diagnosed is more or less likely for patients with COVID-19 than for those with a negative SARS-CoV-2 test, retrospective participation may lead to spurious associations.

Our study had several limitations (Hernandez-Diaz et al., 2022). First, approximately 95% of the participants enrolled during pregnancy were lost to follow-up. This raises concerns about selection bias if the characteristics of those who were lost were different from the remaining participants and associated with the outcomes. However, the baseline characteristics of participants who were lost to follow-up were similar to those of the observed cohort. Nonetheless, the reduction in sample size severely affected the precision of our estimates. With the small number of pregnancies contributing to the analysis we can only rule out large teratogenic effects. Although the upper bound of the 95% confidence interval in our primary analysis was 4.4, the optimal analysis suggests that a 5-fold or even greater increase in the risk of MCM after first-trimester maternal SARS-CoV-2 exposure has not been ruled out.

Second, the IRCEP collected information directly from study participants. Accuracy of recall was facilitated by using structured questionnaires, detailed questions that allowed only plausible responses, and calendars to

| **Kidney, urinary tract** | Tested negative n = 72 | SARS-CoV-2 infection during first trimester n = 5 |
|--------------------------|------------------------|-----------------------------------------------|
|                          | Cystic kidneys, dysplastic kidney |                             |
|                          | Patent foramen ovale, horseshoe kidney* |                             |
|                          | Hydronephrosis (\times 2) |                             |
|                          | Renal agenesis (\times 2) |                             |
|                          | Renal malformation |                             |
|                          | Vesicoureteral and renal malformation |                             |
|                          | Vesicoureteral malformation |                             |
| **musculoskeletal anomalies** | Craniosynostosis (\times 2) | Omphalocele |
|                          | Diaphragmatic hernia (\times 2) |                             |
|                          | Ingual hernia (in term female) |                             |
| **Limb** | Club foot (\times 2) | Leg length discrepancy |
|                          | Missing fingers, joint deformity |                             |
|                          | Hand malformation |                             |
|                          | Hip dysplasia (\times 5) |                             |
|                          | Joint deformity (\times 2) |                             |
|                          | Limb deformity |                             |
|                          | Webbing of fingers (\times 2) |                             |

*Note: SARS-CoV-2 positive cases are those with first-trimester positive PCR tests or COVID-19 symptom onset in the first trimester with clinical diagnosis and/or serology testing. Rows with asterisks indicate a case with multiple anomalies repeated in another row within a different organ system.
help establish gestational timing and enhance recall of dates (Mitchell et al., 1986). We anticipate that presence of MCMs would be remembered by mothers, who were specifically asked about them on multiple occasions during the study. If the mother reported a potential problem with the fetus or newborn, a list of specific malformations organized by organ system was provided to assist recall. If present, misclassification of malformations could be differential between COVID-19 cases and the reference group. Concern that COVID-19 might pose a risk could lead to more prenatal diagnostic measures, such as ultrasound, and more careful examination of infants for defects postnatally, potentially leading to differential accuracy in detection and classification of defects among exposed and unexposed. However, we focused on MCMs, which are less vulnerable to differential misclassification, and better ascertainment in pregnancies with COVID-19 would tend to overestimate the relative risk. Therefore, although misclassification of MCMs may have occurred, it is unlikely that it would have hidden a true major teratogenic effect.

Third, enrollment in the study was voluntary and required access to internet connection. Therefore, participants are not a random sample of all women with COVID-19. Consequently, the characteristics and experience of study participants may differ from those not participating, and these characteristics could theoretically modify the effects of SARS-CoV-2. However, biological effects of viruses in organogenesis tend to be universal and not modified by volunteerism or characteristics associated with it (e.g., socioeconomic status, literacy, internet connectivity). Fourth, when assessing the effect of SARS-CoV-2 on pregnancy outcomes in observational studies, an association could be explained by a direct effect of the virus, an effect mediated through maternal symptoms (e.g., pneumonia or fever) or confounding (e.g., women susceptible to infection are also at high risk of adverse pregnancy outcomes). However, the distribution of risk factors for MCMs was similar between the exposed and reference groups.

CONCLUSION

Our findings provide no evidence of a large teratogenic effect associated with maternal SARS-CoV-2 infection during the first months of pregnancy, but larger studies are necessary to draw firm conclusions.

FUNDING INFORMATION

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CONFICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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