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Review Paper

Impacts of COVID-19 pandemic on preterm birth: a systematic review and meta-analysis

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Abstract

Objectives: The COVID-19 pandemic has significantly affected healthcare systems and daily well-being. However, the reports of the indirect impacts of the pandemic on preterm birth remain conflicting. We performed a meta-analysis to examine whether the pandemic altered the risk of preterm birth.

Study design: This was a systematic review and meta-analysis of the previous literature.

Methods: We searched MEDLINE and Embase databases until March 2022 using appropriate keywords and extracted 63 eligible studies that compared preterm between the COVID-19 pandemic period and the prepandemic period. A random effects model was used to obtain the pooled odds of each outcome. The study protocol was registered with PROSPERO (No. CRD42022326717).

Results: The search identified 3827 studies, of which 63 reports were included. A total of 3,220,370 pregnancies during the COVID-19 pandemic period and 6,122,615 pregnancies during the prepandemic period were studied. Compared with the prepandemic period, we identified a significant decreased odds of preterm birth (PTB; <37 weeks’ gestation; pooled odds ratio [OR; 95% confidence interval (CI)] = 0.96 [0.94, 0.98]; I^2 = 78.7%; 62 studies) and extremely PTB (<28 weeks’ gestation; pooled OR [95% CI] = 0.92 [0.87, 0.97]; I^2 = 26.4%; 25 studies) during the pandemic, whereas there was only a borderline significant reduction in the odds of very PTB (<32 weeks’ gestation; pooled OR [95% CI] = 0.93 [0.86, 1.01]; I^2 = 90.1%; 33 studies) between the two periods. There was significant publication bias for PTB.

Conclusion: Pooled results suggested the COVID-19 pandemic was associated with preterm birth, although there was only a borderline significant reduction for very PTB during the pandemic compared with the prepandemic period. Large studies showed conflicting results, and further research on whether the change is related to pandemic mitigation measures was warranted.

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Introduction

The COVID-19 pandemic has resulted in substantial morbidity and mortality and also created a profound impact on healthcare systems, social functioning, and daily well-being. 1,2 To restrict the spread of the disease, countries imposed national or regional lockdowns, which consisted of multiple restrictions measures, including stay-at-home orders, working at home, healthcare disruption, and school or shop closure except for emergency services. 3,4 The widespread lockdown is unprecedented, and the impact on human physical and mental health is not fully understood. 5

Previous studies have found that the COVID-19 pandemic may have influenced obstetric interventions and birth outcomes due to the disruption of maternal and neonatal health services and massive stress from psychosocial and economic consequences of the pandemic. 6,7 Most attention has been paid to the impact of the pandemic on preterm birth (PTB), but with inconsistent results and insufficient analysis. Reductions in PTB rates during the COVID-19 pandemic compared with before the pandemic have been reported in many countries, such as Australia, 8 the United States, 9–12 Israel, 13,14 England, 15 Denmark, and Ireland, 16,17 whereas studies in China, the Netherlands, and Spain have not found such changes. 18–20 Vaccaro et al. 21 reported no difference in the risk of PTB (<37 weeks’ gestation) during the pandemic compared with
the prepandemic period based on a rapid review of 13 studies. In other studies, preterm was not significantly changed overall but was decreased in high-income countries, and Yang et al. only found a significantly reduced risk in the data from unadjusted estimates and single-center studies. However, the indirect effect of the COVID-19 pandemic on PTB may be affected by more confounding factors, such as sample size, countries, study population, comparative period (seasonality), and study quality. A comprehensive and thorough study with further subgroup analysis for these factors is needed to assess the association between the pandemic and preterm.

Given the inconsistent conclusions from previous studies, the meta-analysis of these articles was conducted to estimate the impact of the global COVID-19 pandemic on PTB and further assess the confounding factors’ effects by subgroup analysis.

**Methods**

We conducted a meta-analysis of previous studies to determine the effects of the COVID-19 pandemic on preterm delivery. This review was performed according to the Preferred Reporting Items in Systematic Reviews and Meta-analyses (PRISMA) guidelines. The study protocol was registered with PROSPERO (No. CRD42022326717).

**Sources: Search strategy and selection criteria**

We electronically retrieved MEDLINE and Embase databases up to March 2022 for relevant articles. The following terms were used in the search: “preterm” or “premature” or “PTB” in combination with “2019-nCoV” or “COVID-19” or “SARS-COV-2”. Studies were included if (1) PTB was compared between the pandemic period vs the prepandemic period; (2) effect size (odds ratios [ORs] or risk ratios [RRs]) with 95% confidence interval (CI) was provided or could be calculated; (3) published in English. We excluded studies that were case reports or not published as full reports; studies with wrong study design (women with SARS-COV-2 infection were not excluded or the outcomes were not compared in general populations) or without control subjects (only reports on the rate of preterm during the pandemic) or with inappropriate comparison groups; studies of only SARS-COV-2 infected women.

**Quality assessment**

Sixty-three eligible studies included in this study were scored according to the Newcastle–Ottawa Scale. Quality assessment of these studies was based on three categories: selection, comparability, and outcomes. The studies with scores ranged from 0 to 9; those with a score of 0–3 were considered to have a high risk of
bias, 4–6 had a moderate risk of bias, and 7–9 had a low risk of bias, respectively.

Statistical analyses

The following data were extracted: authors, publication date, study design, sample size, study population, pandemic period definition, prepandemic period definition, effect size, and other related information. For studies adopting multivariate logistic regression for adjustment of confounders, we extracted adjusted OR and 95% CI. Otherwise, we calculated OR and 95% CI based on the extracted data for unadjusted studies. The outcome of interest in this review was preterm. Furthermore, we calculated preterm birth (<37 weeks of gestation), very PTB (<32 weeks of gestation), and extremely PTB (<28 weeks of gestation) based on the clinician’s best estimate of gestational age. A random effects model was used to obtain the pooled odds of each outcome. Statistical heterogeneity among studies was evaluated using the Chi-squared test, I² statistics, and P values. The small study effects were assessed by funnel plots, and asymmetry was assessed with Egger’s test.

We conducted a subgroup analysis for factors that could potentially affect the association between the pandemic and PTB: effect size (adjusted OR or crude OR), sample size (<10,000; 10,000–100,000; or ≥100,000), study population (single center, multicenter, or regionwide/nationwide), country classification (low-/middle-income or high-income country according to World Bank classifications), published year (2020, 2021, or 2022), prepandemic period definition (equivalent period in previous years or near before the lockdown period), and quality assessment of included studies (moderate or low risk of bias). In addition, we performed sensitivity analysis by omitting each study individually and recalculating the pooled effect size estimates for the remaining studies to assess the effect of individual studies on the pooled results. All statistical analyses were two sided and performed using STATA software (Version 11.0; Stata Corp; College Station; USA).

Results

Initially, 3827 studies were retrieved, and 63 previously published articles were eligible for inclusion with further screening. There were 62 reports provided data on the odds of PTB during the pandemic compared with the prepandemic period, 33 reports included the odds of VPTB, and 25 studies included the data of EPTB (Fig. 1). Table S1 in the supplementary material shows the characteristics of included studies in the quantitative synthesis. All the studies used a historical cohort design. A total of 3,220,370 pregnancies during the COVID-19 pandemic period and 6,122,615 pregnancies during the prepandemic period were studied. Twenty-nine countries were...
represented, with substantial variation in pandemic mitigation measures among countries. There were 31 reports from single-center studies, 12 multicenter studies, and 14 national registries, and the remaining six were regional reports. The duration of the “pandemic period” studied varied from 1 month to 15 months, and the duration of the “prepandemic period” studied varied from 2 months to 15 years. And the sample sizes varied from 81 to 2,219,914 pregnancies. The scores of quality assessments of the studies ranged from 5 to 9 (Table S2). There were 33 articles with moderate risk of bias and 30 articles with low risk of bias.

PTB (<37 weeks of gestation) was reported in 62 studies. There was a significant reduction in the rate of PTB during the pandemic period compared with the prepandemic period (pooled OR [95% CI] = 0.96 [0.94, 0.98], I² = 78.7%, 62 studies; Fig. 2). Test for heterogeneity among subgroups revealed significant differences besides effect size and prepandemic period (P < 0.1). VPTB (<32 weeks of gestation) was reported in 33 studies with varying gestational weeks thresholds and conflicting findings. There was a reduction in the odds of VPTB with a borderline significance (pooled OR [95% CI] = 0.93 [0.86, 1.01], I² = 90.1%, 33 studies; Fig. 3). Further heterogeneity test showed significant difference among subgroups (P < 0.1). Twenty-five studies reported EPTB (<28 weeks of gestation), which showed a significant decrease in EPTB (pooled OR [95% CI] = 0.92 [0.87, 0.97], I² = 26.4%, 25 studies; Fig. 4). Then subgroups analyses suggested that there was no heterogeneity (P > 0.1). Moreover, we found evidence of a small study effect for PTB (Egger’s P = 0.018) but not for VPTB (Egger’s P = 0.235) and EPTB (Egger’s P = 0.441; Fig. 5).

In the sensitivity analysis, the pooled estimates of PTB and EPTB were not significantly changed when a study was omitted, suggesting that no one study had a large effect on the pooled estimate. However, for VPTB, when study conducted by Main et al. was omitted, the result became significant, and the heterogeneity became non-significant (pooled OR [95% CI] = 0.93 [0.90, 0.97], I² = 27.2%).

Discussion

The present meta-analysis aimed to investigate and systematically analyze the relationship between the COVID-19 pandemic and PTB. We specifically excluded articles that only reported outcomes of the pregnant population infected with COVID-19. The indirect impact of the COVID-19 lockdown on preterm was more noticed. The results showed the significant reduction in PTB and EPTB but
no difference in VPTB during the pandemic compared with before the pandemic.

In this meta-analysis, PTB was significantly decreased overall, but the previous meta-analysis reported by Chmielewska et al.,\textsuperscript{22} Vaccaro et al.,\textsuperscript{21} and Yang et al.\textsuperscript{23} suggested no differences in pooled ORs. Further subgroups analysis, Chmielewska et al.\textsuperscript{22} found PTB was decreased in high-income countries, and Yang et al.\textsuperscript{23} found the reduction of PTB was only noted in unadjusted estimates and single-center studies. Moreover, they reported no reduction in unadjusted odds of PTB <34 weeks', <32 weeks', and <28 weeks' gestation. Inconsistency among conclusions from different studies and a lack of detailed evidence to inform the effects of the COVID-19 pandemic on VPTB and EPTB prompted us to conduct a more specifically quantitative synthesis.

| Study subgroup        | Odds Ratios (95% CI) |
|-----------------------|----------------------|
| **Effect size**       |                      |
| Crude OR (n = 20)     | 0.92 (0.87, 0.97)    |
| Adjusted OR (n = 5)   | 0.90 (0.76, 1.07)    |
| **Sample size**       |                      |
| Simple size < 10,000 (n = 11) | 0.87 (0.65, 1.17) |
| 10,000 ≤ Sample size < 100,000 (n = 6) | 0.83 (0.64, 1.06) |
| Sample size ≥ 100,000 (n = 8) | 0.92 (0.90, 0.95) |
| **Study population**  |                      |
| Single center (n = 10) | 0.88 (0.79, 0.97) |
| Multicenter (n = 6)   | 1.00 (0.75, 1.32)   |
| Regionwide or Nationwide (n = 9) | 0.93 (0.87, 0.98) |
| **Country classification** |                  |
| Low and middle income countries (n = 5) | 0.92 (0.87, 0.96) |
| High income countries (n = 20) | 0.92 (0.86, 0.99) |
| **Published year**    |                      |
| 2020 (n = 3)          | 0.83 (0.45, 1.55)   |
| 2021 (n = 21)         | 0.90 (0.85, 0.96)   |
| 2022 (n = 1)          | 0.92 (0.88, 0.97)   |
| **Pre-pandemic period** |                  |
| Equivalent period in previous years (n = 20) | 0.91 (0.86, 0.97) |
| Near before the lockdown period (n = 5) | 0.94 (0.78, 1.14) |
| **Quality Assessment of the studies (NOS)** |                  |
| Moderate risk of bias (n = 15) | 0.88 (0.81, 0.96) |
| Low risk of bias (n = 18) | 0.93 (0.87, 0.99) |
| **Overall** (I-squared = 26.4%, P = 0.112) | 0.92 (0.87, 0.97) |

Statistic method: random effect model

**Fig. 4.** Forest plot for odds of extremely preterm birth <28 weeks' gestation.

**Fig. 5.** Funnel plots for studies reporting on preterm birth.
We identified an overall reduction in the odds of PTB during the pandemic compared with before the pandemic. However, the further subgroup analysis showed there was no difference in PTB in specific subgroups, such as the data from adjusted odds, the studies from multicenter or low- and middle-income countries, and the prepandemic period defined as near before the lockdown. There could be several reasons for this conflict, such as the heterogeneity of the study populations, variation in sample sizes, lengths or definition of the pandemic and prepandemic periods, and the quality of studies. In addition, the significant statistical heterogeneity was also partly explained by the methodological heterogeneity of the studies and the variation in lockdown measures among countries based on the results of subgroup analysis.

The researchers have proposed that COVID-19–related lockdown may cause socioenvironmental and behavioral modifications, including maternal workload reduction, improved air quality, reduced maternal non-COVID-19–related infections, reductions in physical activity, and better nutritional support, thus playing a role in pregnancy prolongation and exert a beneficial impact on PTB.13,15,50,66 On the other hand, several recent studies have shown that COVID-19 pandemic–related stressors and quarantine measures have exacerbated perinatal anxiety and depression.5,23 Stress, worries, and anxieties during pregnancy are often associated with PTB.23 Moreover, COVID-19 lockdown may result in a reduction in antenatal care and fetal surveillance. Therefore, the impact of the pandemic on PTB is a double-edged sword. And for the risk of VPTB, there was no overall difference during the pandemic, but analyses of adjusted odds and 10,000 ≤ sample size ≤ 100,000 studies only suggested VPTB might be reduced. Furthermore, we found the high heterogeneity disappeared for VPTB, and the risk of VPTB became significant reduction when the study of Main et al.10 was omitted. The study reported the preterm and the de

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