



COVID-19 pandemic and population-level pregnancy and neonatal outcomes: a living systematic review and meta-analysis

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Abstract

Introduction: Conflicting reports of increases and decreases in rates of preterm birth (PTB) and stillbirth in the general population during the COVID-19 pandemic have surfaced. The objective of our study was to conduct a living systematic review and meta-analyses of studies reporting pregnancy and neonatal outcomes by comparing the pandemic and pre-pandemic periods.

Material and methods: We searched PubMed and Embase databases, reference lists of articles published up until 14 May 2021 and included English language studies that compared outcomes between the COVID-19 pandemic time period and pre-pandemic time periods. Risk of bias was assessed using the Newcastle–Ottawa scale. We conducted random-effects meta-analysis using the inverse variance method.

Results: Thirty-seven studies with low-to-moderate risk of bias, reporting on 1 677 858 pregnancies during the pandemic period and 21 028 650 pregnancies during the pre-pandemic period, were included. There was a significant reduction in unadjusted estimates of PTB (28 studies, unadjusted odds ratio [uaOR] 0.94, 95% confidence [CI] 0.91–0.98) but not in adjusted estimates (six studies, adjusted OR [aOR] 0.95, 95% CI 0.80–1.13). The reduction was noted in studies from single centers/health areas (uaOR 0.90, 95% CI 0.86–0.94) but not in regional/national studies (uaOR 0.99, 95% CI 0.95–1.03). There was reduction in spontaneous PTB (five studies, uaOR 0.89, 95% CI 0.82–0.98) and induced PTB (four studies, uaOR 0.90, 95% CI 0.81–1.00). There was no reduction in PTB when stratified by gestational age <34, <32 or <28 weeks. There was no difference in stillbirths between the pandemic and pre-pandemic time periods (21 studies, uaOR 1.08, 95% CI 0.94–1.23; four studies, aOR 1.06, 95% CI 0.81–1.38). There was an increase in birthweight (six studies, mean difference 17 g, 95% CI 7–28 g) during the pandemic period. There was an increase in maternal mortality (four studies, uaOR 1.15, 95% CI 1.05–1.26), which was mostly influenced by one study from Mexico. There was significant publication bias for the outcome of PTB.

Abbreviations: ELBW, extremely low birthweight; GA, gestational age; LBW, low birthweight; PTB, preterm birth; VLBW, very low birthweight.

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Conclusions: The COVID-19 pandemic time period may be associated with a reduction in PTB; however, referral bias cannot be excluded. There was no difference in stillbirth between the pandemic and pre-pandemic period.

KEYWORDS

birthweight, epidemic, maternal mortality, neonatal mortality, preterm birth, SARS-CoV-2, stillbirth, stress

1 | INTRODUCTION

Although most pregnancies end with healthy mothers and healthy children, a small proportion result in adverse outcomes for the mother, fetus or neonate. Among others, such outcomes include stillbirth, preterm birth (PTB), neonatal mortality and maternal mortality—all of which can have devastating and long-lasting effects on families.^{1–3} Preterm birth (birth before 37 weeks' gestation) is a major determinant of neonatal mortality and morbidity⁴ with long-term adverse consequences during childhood and adulthood.⁵ Medical, social, psychological, environmental and economic factors have all been implicated in the etiopathogenesis of PTB and other adverse pregnancy outcomes.

The COVID-19 pandemic has had an unprecedented impact on society worldwide and has provided a natural experiment allowing us to study the effects of these factors on adverse pregnancy outcomes. During the early stages of the pandemic, reports emerged describing reduced PTB rates in Denmark⁶ and Ireland.⁷ However, these were followed by reports of increased PTB rates (births between 28 and 32 weeks' gestation) in Nepal⁸ and no changes in PTB rates in the UK⁹ and Sweden.¹⁰ At the same time, increases in stillbirth rates were reported from the UK⁹ and Nepal,⁸ with or without changes in PTB rates, while no change in the stillbirth rate was reported from Ireland.²

In light of these mixed reports, it is uncertain whether the COVID-19 pandemic has affected pregnancy outcomes at the population level. Inconsistency among conclusions from different studies and a lack of evidence to inform the creation of evidence-based population health guidance prompted us to undertake a comprehensive review of the influence of the COVID-19 pandemic on pregnancy outcomes. Our objective was systematically to review and meta-analyze studies reporting defined local, regional or national population-based rates for maternal, fetal and neonatal outcomes during the pandemic period compared with the pre-pandemic period.

2 | MATERIAL AND METHODS

The review was conducted using standardized methods for systematic reviews of observational studies and reported according to the Preferred Reporting Items in Systematic Reviews and Meta-analyses guidelines.¹¹ No ethical approval was obtained, as all data used for

Key message

Population-level preterm birth may have declined during the pandemic but there was no difference in stillbirths. The reduction was only noted in single-center studies and in unadjusted estimates, raising the possibility of referral bias and need for further data.

these analyses were published previously. The review protocol was registered in PROSPERO (CRD42021234036).¹²

2.1 | Data sources: search strategy and selection criteria

We searched PubMed and Embase databases, reference lists of included articles, and personal files for studies published up to 14 May 2021. The search strategy used a combination of the MeSH terms “preterm” or “stillbirth” AND “Covid19” or “SARS-COV-2” and included any type of study design published in the English language (Appendix S1). Since this is a living systematic review, it will be updated 3-monthly for the duration of the pandemic, using the same search strategy. Studies were included if they compared pregnancy outcomes between the COVID-19 pandemic time period versus pre-pandemic time periods and reported on any of the outcomes of interest. We excluded studies that only reported outcomes of pregnant women with COVID-19 infection. Screening of articles was conducted by two authors (PS and JY) and disagreements were resolved through discussion (JY, RD and PS) and consensus. Since we were interested in overall pregnancy outcomes, we did not restrict studies based on plurality (included singleton and multiple pregnancies).

2.2 | Exposure

In most studies, the pandemic period was defined as the period of time beginning from the date or month of the implementation of emergency lockdown measures in relevant countries or states or cities, or when there was an emergence of cases or a surge of cases in the population studied. Some studies assessed the “post-lockdown”

period, which for the purpose of this study was included as “pandemic” period, as we are still not out of pandemic. The pre-pandemic period was defined either as the period ending immediately before lockdown measures were implemented or before the emergence of the first case or high case numbers in the population, or as a historical period, such as births in the same population in previous year(s). The lengths of these periods varied across studies.

We included studies that reported outcomes of pregnancy in general population. The review was not designed to evaluate outcomes of pregnancies where only women were affected by SARS-CoV-2 infection were reported.

2.3 | Outcomes

The primary outcomes in this study were rates of PTB and stillbirth. Secondary outcomes included mean birthweight (continuous) and rates of low birthweight (LBW), spontaneous PTB, medically indicated PTB, and neonatal, perinatal or maternal mortality. We contacted authors to obtain data on stillbirth and neonatal mortality when the outcomes were reported as “intrauterine fetal death” (IUFD) and “perinatal mortality”. The outcomes of IUFD and perinatal mortality, though specified in the protocol, were not included ultimately in review (deviation from protocol). Outcomes were defined as follows:

1. Preterm birth: Live births between 22+0 and 36+6 weeks' gestation were classified as PTB. Data on PTB at <28 weeks', <32 weeks' and <34 weeks' gestation were reported separately in some studies and were analyzed independently.
2. Stillbirth: Death before the complete expulsion or extraction from the parturient of a product of human conception at or after 20 weeks' gestation.¹³
3. Birthweight: Infant weight in grams, measured as soon as possible after live birth. Birthweight <2500 g was defined as LBW, birthweight <1500 g was defined as very low birthweight (VLBW), and birthweight <1000 g was defined as extremely low birthweight (ELBW).
4. Spontaneous PTB: Birth of a baby between 22+0 and 36+6 weeks' gestation following spontaneous preterm labor or preterm pre-labor rupture of membranes.³
5. Medically indicated PTB: Preterm birth initiated by a healthcare provider for maternal or fetal indications.³
6. Neonatal mortality: Death of a newborn due to any cause before 28 days of age.
7. Maternal mortality: Death of a woman either during pregnancy or childbirth from any cause related to or aggravated by pregnancy or its management, or within 42 days of end of pregnancy, irrespective of the duration and site of the pregnancy.⁹

2.4 | Data extraction and risk of bias assessment

Data from the eligible studies were independently extracted by two authors (JY and PS) using a predefined, standardized

extraction form. Disagreements between the authors were resolved by consensus and involving a third author (RD). The information extracted included details of the publication, study setting and size, pre-pandemic period definition, pandemic period definition, and rates of the reported outcomes in pre-pandemic and pandemic time periods. We relied only on published information.

We anticipated that primarily observational studies would be included in this review; thus, we used the Newcastle–Ottawa Scale¹⁴ for cohort studies to assess risk of bias. This scale assesses risk of bias in domains of selection, comparability and outcomes, and assigns a maximum score of 9. Studies with scores of 0–3 were considered to have a high risk of bias, those with scores of 4–6 a moderate, and those with scores of 7–9 a low risk.

2.5 | Statistical analyses

We planned for meta-analyses of studies that reported similar outcomes and were methodologically homogeneous. For binary outcomes, we calculated the summary unadjusted odds ratios (uaOR), adjusted OR (aOR) when available and 95% confidence intervals (CI), whereas for birthweight we calculated the mean difference (MD) and 95% CI. Statistical heterogeneity was assessed using Cochran's Q statistic and quantified by calculating the I^2 values. We expected clinical and methodological heterogeneity between studies and thus planned a priori for random effect meta-analyses using the inverse variance method. We planned to meta-analyze adjusted estimates from studies that reported them, understanding that studies will have adjusted for different factors based on data availability and baseline differences. We also expected that the duration of the “pre-pandemic” period would vary across studies; we therefore conducted meta-regression on the variable “duration of the pre-pandemic period” as a covariate to explain any heterogeneity in the results. Post-hoc subgroup analyses were conducted for the two primary outcomes after dividing studies into single-center (or selected hospitals/centers in an area), regional (statewide or province-wide) or national in scope. Publication bias was assessed qualitatively using funnel plots, and quantitatively by calculating Egger's regression intercept when >10 studies were included in the meta-analyses. For the Egger test, values of <0.10 were considered indicative of publication bias. Meta-analyses were conducted using Stata v11.0 (Statacorp 2009, College Station, TX, USA) and Review Manager v5.3 (Nordic Cochrane Center, Copenhagen, Denmark).

3 | RESULTS

3.1 | General study characteristics

Of 9123 records in the initial search, 37 articles were eligible for inclusion, of which 36 were used in the quantitative synthesis^{2,6-10,15-44} (Figure 1). Eighteen full-text reports were excluded: reasons for the exclusions are provided in Appendix S2. For one study conducted in the Netherlands by Been et al.,⁴⁵ data were presented using multiple

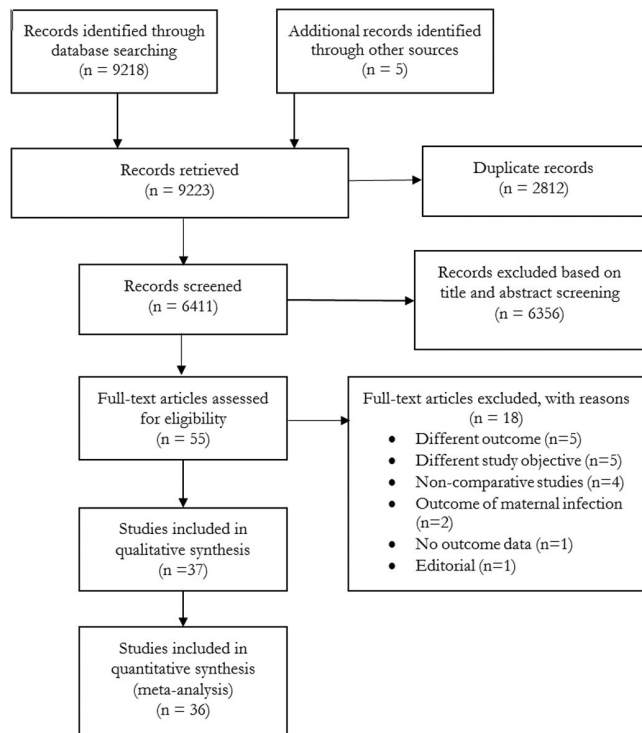


FIGURE 1 PRISMA flow diagram: article selection

cut-offs to define the pre- and post-pandemic periods, with several different comparisons, making it difficult to select one comparison that aligned well with the other studies; we therefore included this study in the systematic review but not in meta-analyses. Khalil et al.⁹ had data for stillbirth outcome that overlapped with another study; however, preterm birth data were not overlapping, so only preterm birth data were used in this review. Study characteristics are reported in Table 1: six studies were national in scope, seven were regional, and 24 were local, including single-center studies. Across the included studies, 1 677 858 pregnancies during the pandemic period (excluding numbers from Been et al.⁴⁵) and 21 028 650 pregnancies during the pre-pandemic period were studied. Duration of the "pandemic period" studied varied from 4 weeks to 7 months, and duration of the "pre-pandemic period" studied varied from 2 months to 19 years. The risk of bias assessment scores for the included studies ranged from 5 to 9 (Table 2). Twenty studies had moderate risk of bias and 17 studies had low risk of bias. Twenty-nine studies included a pregnant population from local/regional/national data which may have included those with COVID-19 infection, whereas eight studies specifically excluded women with COVID-19 infection if it was known. However, it is difficult to be completely certain, as testing on pregnant women was not universally applied in any of the studies.

3.2 | Synthesis: outcomes

Preterm birth and its subgroups: Twenty-eight studies including 300 117 women during the pandemic period and 1 268 708 women

in the pre-pandemic period reported PTB <37 weeks' gestation; there was a reduction in unadjusted odds of PTB during the pandemic period compared with the pre-pandemic period (pooled uaOR 0.94, 95% CI 0.91–0.98, $I^2 = 62\%$; Figure 2). However, subgroup analyses revealed no differences in odds of PTB during pandemic period in national or regional studies (uaOR 0.99, 95% CI 0.94–1.03, $I^2 = 76\%$). There was a reduction in odds of PTB in single-center studies (uaOR 0.90, 95% CI 0.86–0.94, $I^2 = 12\%$, subgroup differences $p = 0.005$; Figure 2). Six of these studies reported adjusted estimates (with different factors adjusted, reported in Table 1) but pooled analyses did not show significant differences in PTB rate (pooled aOR 0.95, 95% CI 0.80–1.13; $I^2 = 92\%$; Figure 3). There was no reduction in unadjusted odds of PTB <34 weeks' (Table 3, Appendix S3), <32 weeks' (Table 3, Appendix S4), and <28 weeks' gestation (Table 3, Appendix S5). Meta-analysis of five studies reporting data on spontaneous PTB (Table 3, Appendix S6), and four studies of medically indicated PTB revealed reduction in unadjusted odds of PTB during pandemic period (Table 3, Appendix S7).

Most of the studies presented data for the entire pregnant population, but some categorically excluded individuals with a known confirmed diagnosis of COVID-19. When the latter studies were included in meta-analyses, we could identify no difference in PTB or stillbirth. For PTB, regional/national data from two studies had a pooled uaOR of 1.05 (95% CI 0.87–1.26) and six single-center studies had a pooled uaOR of 0.89 (95% CI 0.79–1.01). For stillbirths, regional/national data from two studies had a pooled uaOR of 1.14 (95% CI 0.58–2.22 and four single-center studies had a uaOR of 1.97 (95% CI 0.85–4.55).

Stillbirth: Twenty-one studies of 237 381 women during the pandemic period and 633 050 women in the pre-pandemic period assessed stillbirth. There was no difference in the odds of stillbirth between the pandemic and pre-pandemic periods (pooled uaOR 1.08, 95% CI 0.95–1.23, $I^2 = 62\%$; Figure 4). Subgroup analyses also revealed no difference in stillbirth during the pandemic period vs the pre-pandemic period in single-center studies and regional/national studies (Figure 4). Meta-analysis of adjusted estimates from four studies revealed no difference in stillbirth between groups (aOR 1.06, 95% CI 0.81–1.38; $I^2 = 72\%$; Appendix S8).

Birthweight: Seven studies of 13 871 women during the pandemic period and 49 152 women in the pre-pandemic period reported birthweight. There was an increase in mean birthweight during the pandemic compared with the pre-pandemic period (pooled mean difference 17 g, 95% CI 7–28 g, $I^2 = 0\%$; Table 3, Appendix S9). There was no difference in odds of low birthweight (Table 3, Appendix S10), very low birthweight (Table 3, Appendix S11) or extremely low birthweight (Table 3, Appendix S12).

Neonatal mortality: Six studies of 90 976 neonates during the pandemic period did not show any difference in the rate of neonatal mortality between the pandemic and pre-pandemic periods (uaOR 1.34, 95% CI 0.71–2.55, $I^2 = 96\%$; Table 3, Appendix S13); however, the heterogeneity of results across studies was very high. One national study from nine hospitals in Nepal⁸ reported

TABLE 1 Characteristics of included studies

First Author, Country	Population level	Neonatal	Exposed cohort (Pandemic period)	Non-exposed cohort (Pre-pandemic period)	Outcomes	Statistical approach	Factors adjusted for, if any
Arnaez, ¹⁵ Spain	13 regional hospitals	Singleton	15 March–3 May 2020	15 March–3 May 2015–2019	PTB <37 weeks; PTB <32 weeks; PTB <28 weeks; Stillbirth; LBW; VLBW; ELBW	Jointpoint regression analysis; Multivariate binomial logistic regression models	Hospital, sex, type of delivery and multiples
Been, ⁴⁵ Netherlands	Nationwide	Singleton	1 month, 2 months, 3 months and 4 months after 9 March 2020; 1 month, 2 months, 3 months and 4 months after 15 March 2020; 1 month, 2 months, 3 months and 4 months before 23 March 2020	1 month, 2 months, 3 months and 4 months before 9 March 2020; 1 month, 2 months, 3 months and 4 months before 15 March 2020 1 month, 2 months, 3 months and 4 months before 23 March 2020	PTB <37 weeks; PTB <32 weeks	Difference-in-regression-discontinuity analysis	
Berghella, ¹⁶ USA	Single center	Singleton	1 March – 31 July 2020	1 March – 31 July 2019	PTB <37 weeks; PTB <34 weeks; PTB <28 weeks; Stillbirth; Spontaneous PTB; Medically indicated PTB	Chi square test; multivariable logistic regression	
Caniglia, ¹⁷ Botswana	Nationwide	Singleton	3 April – 20 July 2020	3 April – 20 July 2017–2019	PTB <37 weeks; PTB <32 weeks; Stillbirth; Neonatal mortality	Difference-in-differences	
De Curtis, ¹⁸ Italy	Single center	Singleton	March–May 2020	March–May 2019	PTB <37 weeks; PTB <32 weeks; Stillbirth	Z test	
Dell'Utri, ¹⁹ Italy	Single center	Not reported	23 February–24 June 2020	23 February–24 June 2019	Stillbirth	Chi-square test	
Du, ²⁰ China	Single center	Singleton	20 January–31 July 2020	20 May–30 November 2019	PTB <37 weeks; Stillbirth; LBW	Chi-square test; t test; Univariate and multivariate log-binomial regression models	Age, ethnicity, occupation, education, gravidity, parity, h/o miscarriage, h/o induced abortion, BMI, GWG, f/h chronic diseases, prenatal visits
Goyal, ²¹ India	Single center	Not reported	1 April – 30 August 2020	1 October 2019–29 February 2020	Maternal mortality	Chi-square test; Student's t test	

(Continues)

TABLE 1 (Continued)

First Author, Country	Population level	Neonatal	Exposed cohort (Pandemic period)	Non-exposed cohort (Pre-pandemic period)	Outcomes	Statistical approach	Factors adjusted for, if any
Greene, ²² USA	Single center	Not reported	March–April 2020	January–February 2020	PTB <37 weeks	Student's t test; Wilcoxon test; Chi-square test; Fisher's exact test	
Gu ²³ China	Single center	Not reported	January–February 2020	January–February 2019	PTB <37 weeks; Stillbirth; Birthweight	t test; Chi-square test	
Handley, ²⁴ USA	2 Penn Medicine hospitals in Philadelphia	Singleton	March–June 2020	March–June 2018–2019	PTB <37 weeks; Stillbirth; Spontaneous PTB; Medically indicated PTB	Fisher exact	
Harvey, ²⁵ USA	Regionwide	Not reported	22 March–30 April 2020	22 March–30 April 2015–2019	PTB <37 weeks; PTB <32 weeks; LBW; VLBW	Logistic regression models	Maternal age, education, race/ethnicity, diabetes, and hypertension
Hedermann, ⁶ Denmark	Nationwide	Singleton	12 March–14 April 2020	12 March–14 April 2015–2019	PTB <37 weeks; PTB <32 weeks; PTB <28 weeks	Logistic regression	
Janevic, ²⁶ USA	Single center	Not reported	March 28–31 July 2020	28 March–31 July 2019	PTB <37 weeks; PTB <32 weeks	Log binomial regression	
Justman, ²⁷ Israel	Single center	Not reported	March–April 2020	March–April 2019	PTB <37 weeks; PTB <32 weeks; Stillbirth; Birthweight	Chi-square and t test or Mann–Whitney U test	
Kasuga, ²⁸ Japan	Single center	Not reported	1 April–30 June 2020	1 April–30 June 2017–2019	PTB <37 weeks	Not reported	
KC, ⁸ Nepal	9 hospitals across seven provinces	Not reported	21 March–30 May 2020	1 January–20 March 2020	PTB <37 weeks; Stillbirth; LBW; Neonatal mortality	Generalized linear model with Poisson regression; Pearson's χ^2	Ethnicity, maternal age, and complication during admission
Khalil, ⁹ UK	Single center	Singleton; twin; triplet	1 February–14 June 2020	1 October 2019–31 January 2020	PTB <37 weeks; PTB <34 weeks; Stillbirth ^a	Mann–Whitney and Fisher exact	
Kirchengast, ²⁹ Austria	Single center	Singleton	March to July 2020	March to July 2005–2019	PTB <37 weeks; PTB <32 weeks; LBW; VLBW; ELBW	t test; Chi-square test; Linear regression	
Kumar, ³⁰ India	Not reported	Not reported	March to September 2020	March to September 2019	Stillbirth; LBW; ELBW; VLBW	Fisher exact test	

(Continues)

TABLE 1 (Continued)

First Author, Country	Population level	Neonatal	Exposed cohort (Pandemic period)	Non-exposed cohort (Pre-pandemic period)	Outcomes	Statistical approach	Factors adjusted for, if any
Kumari, ³¹ India	4 regional hospitals	Not reported	25 March–2 June 2020	15 January–24 March 2020	Stillbirth; Maternal mortality	Not reported	
Lemon, ³² USA	Single center	Singleton	1 April–27 October 2020	1 January 2018–31 January 2020	PTB <37 weeks; PTB <34 weeks; PTB <28 weeks; Spontaneous PTB; Medically indicated PTB	Pearson Chi-square or t tests	
Li, ³³ China	Single center	Not reported	23 January–24 March 2020	1 January 2019–22 January 2020	PTB <37 weeks; Birthweight	Chi-square, t test and Fisher's exact	
Lumbreras-Marquez, ³⁴ Mexico	Nationwide	Not reported	1 January –9 August 2020	2011–2019	Maternal mortality	Not reported	
Main, ³⁵ USA	Statewide	Singleton	April–July 2020	April–July 2016–2019	PTB <37 weeks; PTB <32 weeks; PTB <28 weeks	Logistic regression	
Matheson, ³⁶ Australia	3 regional hospitals	Singleton and multiple pregnancies	July–September 2019	July–September 2020	PTB <37 weeks; PTB <34 weeks; PTB <28 weeks; Stillbirth; Spontaneous PTB; Medically indicated PTB	Interrupted time-series analysis; Auto-regressive integrated moving average (ARIMA) model	
McDonnell, ⁷ Ireland	Single center	Not reported	January–July 2020	January–July 2018–2019	PTB <37 weeks; Stillbirth	Pearson correlation; Chi-square, Fisher's exact test	
Meyer, ³⁷ Israel	Single center	Singleton	20 March –27 June 2020	20 March –27 June 2011–2019	PTB <37 weeks; PTB <34 weeks; PTB <32 weeks; Stillbirth; Birthweight; Neonatal mortality	Multivariate regression	
Meyer, ³⁸ Israel	Single center	Not reported	February–March 2020	February–March 2019	PTB <37 weeks; PTB <34 weeks; Birthweight	Chi-square; Fisher's exact test; Mann-Whitney U test	
Mor, ³⁹ Israel	Single center	Singleton	21 February –30 April 2020	21 February–30 April 2017–2019	PTB <37 weeks; PTB <34 weeks; PTB <28 weeks; Stillbirth; Birthweight	Chi-square test or Fisher's exact test	

(Continues)

TABLE 1 (Continued)

First Author, Country	Population level	Neonatal	Exposed cohort (Pandemic period)	Non-exposed cohort (Pre-pandemic period)	Outcomes	Statistical approach	Factors adjusted for, if any
Pasternak, ¹⁰ Sweden	Nationwide	Singleton	1 April–31 May 2020	1 April–31 May 2015–2019	PTB <37 weeks; PTB <32 weeks; PTB <28 weeks; Stillbirth	Logistic regression	Maternal age, birth country, parity, body mass index and smoking
Phillip, ² Ireland	Region-wide	Not reported	January–April 2020; and March–June 2020	January–April 2001–2019; and March–June 2016–2019	Stillbirth; LBW; ELBW; VLBW	Poisson regression	
Shakespeare, ⁴⁰ Zimbabwe	Single center	Not reported	April–June 2020	January–March 2020	Stillbirth; neonatal mortality; maternal mortality	Not reported	
Simpson, ⁴¹ Canada	Region-wide	Singleton; multiple	15 March–30 September 2020	15 March–30 September 2015–2019	PTB <37 weeks; PTB <32 weeks; PTB <28 weeks; Stillbirth	Univariable and multivariable logistic regression models	
Stowe, ⁴² UK	Nationwide	Not reported	April–June 2020	April–June 2019	Stillbirth	Fisher exact test	
Sun ⁴³ Brazil	Single center		11 March–11 June 2020	11 March–11 June 2019	PTB <37 weeks; LBW	Not reported	
Wood ⁴⁴ USA	4 level 3 or 4 neonatal intensive care units	Singleton	April–July 2020	April–July 2019	PTB <37 weeks; PTB <34 weeks; PTB <32 weeks; PTB <28 weeks; Spontaneous PTB	Not reported	

ELBW, extremely low birthweight, LBW, low birthweight, PTB, preterm birth, VLBW, very low birthweight.

^aData not utilized due to overlapping cohorts.

TABLE 2 Risk of bias assessment using the Newcastle–Ottawa Scale

First author	Selection			Comparability			Outcome			Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts		
Arnaez ¹⁵	☆	☆	☆	☆	☆	☆	☆	☆	7	
Been ⁴⁵			☆	☆		☆	☆	☆	5	
Berghella ¹⁶	☆	☆	☆	☆		☆	☆	☆	7	
Caniglia ¹⁷			☆	☆	☆☆	☆	☆	☆	7	
De Curtis ¹⁸			☆	☆	☆	☆	☆	☆	6	
Dell'Utri ¹⁹	☆	☆	☆	☆		☆	☆	☆	6	
Du ²⁰	☆	☆	☆	☆	☆☆	☆	☆	☆	8	
Goyal ²¹	☆	☆	☆	☆		☆	☆	☆	6	
Greene ²²	☆	☆	☆	☆	☆	☆	☆	☆	7	
Gu ²³	☆	☆		☆	☆		☆	☆	5	
Handley ²⁴	☆	☆	☆	☆	☆☆	☆	☆	☆	9	
Harvey ²⁵	☆	☆	☆	☆	☆	☆	☆	☆	8	
Hedermann ⁶	☆	☆	☆	☆	☆	☆	☆	☆	7	
Janevic ²⁶	☆	☆		☆	☆		☆	☆	5	
Justman ²⁷			☆	☆	☆	☆	☆	☆	6	
Kasuga ²⁸	☆	☆	☆	☆		☆	☆	☆	6	
KC ⁸			☆	☆	☆☆	☆	☆	☆	7	
Khalil ⁹	☆	☆	☆	☆	☆	☆	☆	☆	7	
Kirchengast ²⁹	☆	☆	☆	☆	☆	☆	☆	☆	7	
Kumar ³⁰			☆	☆	☆	☆	☆	☆	6	
Kumar ³¹	☆		☆	☆	☆☆	☆	☆	☆	6	
Lemon ³²	☆	☆	☆	☆	☆	☆	☆	☆	7	
Li ³³			☆	☆	☆	☆	☆	☆	6	
Lumbreras-Marquez ³⁴	☆	☆		☆		☆	☆	☆	6	
Main ³⁵	☆	☆	☆	☆	☆	☆	☆	☆	7	
Matheson ³⁶	☆	☆		☆	☆		☆	☆	5	
McDonnell ⁷	☆	☆		☆	☆	☆	☆	☆	6	
Meyer I ³⁷	☆	☆	☆	☆	☆	☆	☆	☆	6	

(Continues)

TABLE 2 (Continued)

First author	Selection			Comparability		Outcome		Total score	
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?		Adequacy of follow-up of cohorts
Meyer 2 ³⁸	☆	☆	☆	☆	☆	☆	☆	☆	6
Mor ³⁹	☆	☆	☆	☆	☆	☆	☆	☆	6
Pasternak ¹⁰	☆	☆	☆	☆	☆☆	☆	☆	☆	8
Phillip ²	☆	☆	☆	☆	☆	☆	☆	☆	7
Shakespeare ⁴⁰	☆	☆	☆	☆	☆	☆	☆	☆	5
Simpson ⁴¹	☆	☆	☆	☆	☆	☆	☆	☆	8
Stowe ⁴²	☆	☆	☆	☆	☆	☆	☆	☆	8
Sun ⁴³	☆	☆	☆	☆	☆	☆	☆	☆	5
Wood ⁴⁴	☆	☆	☆	☆	☆	☆	☆	☆	6

A study can be awarded a maximum of 1 star for each item within the Selection and Outcome categories. A maximum of 2 stars can be given for comparability.

a higher neonatal mortality rate during the pandemic period that may reflect significant local impact on access to care during the lockdown period.

Maternal mortality: Four studies reported on maternal mortality. Three studies reported no significant difference in maternal mortality; however, one study from Mexico³⁴ reported a significant increase in maternal mortality during pandemic (Figure 5). The study from Mexico contributed to 98.7% of the weight in this analysis and it also reported that significant portion of excess mortality was due to respiratory infections including COVID-19.

In meta-regression analyses, duration of the pre-pandemic period did not emerge as a significant covariate for any outcome ($p > 0.05$ for all outcomes). We found evidence of publication bias for PTB (Egger's $p = 0.001$; Appendix S14) but not for stillbirth (Appendix S15), with fewer studies reporting higher rates of PTB during the pandemic period.

4 | DISCUSSION

In this systematic review and meta-analysis, we identified a reduction in the unadjusted odds of PTB in pandemic compared with pre-pandemic time periods, especially spontaneous PTB and medically indicated PTB. However, in subgroup analyses, a significant reduction in PTB was only observed in single-center studies, not in regional or national studies. Moreover, we identified no difference in the odds of PTB in analysis of studies that reported adjusted estimates, although there was variation in the factors adjusted for across the individual studies. We identified no difference in any other fetal/neonatal outcomes including stillbirths and neonatal mortality, and only a marginal increase of 17 g in mean birthweight during the pandemic period as compared with the pre-pandemic period. The increased incidence of maternal mortality noted in our meta-analysis, was mostly driven by one study from Mexico³⁴ which included deaths due to COVID-19, which emerged as the leading cause of maternal mortality during the pandemic period.

This review was designed to evaluate the impact of the COVID-19 pandemic time period on pregnancy and neonatal outcomes and not to evaluate studies that report only on maternal COVID-19 infection itself, which has been discussed in other reviews.⁴⁶⁻⁴⁸ We specifically excluded studies which only reported outcomes of pregnant population infected with COVID-19. We identified conflicting evidence from the included studies based on whether they were single-center or regional/national studies. There could be a number of reasons for this. In addition to potential referral bias, other potential explanations include variation in sample sizes, outcome definitions, lengths of the pandemic and pre-pandemic periods, differences in timing and enforcement of lockdown orders, failure of some studies to account for natural variation in pregnancy outcomes over time, and dissimilarities among COVID-19 mitigation strategies.^{8,10,17,24,38} Moreover, the study populations were heterogeneous; for example, baseline PTB rates ranged from 4.8% to 16.7% during pre-pandemic period

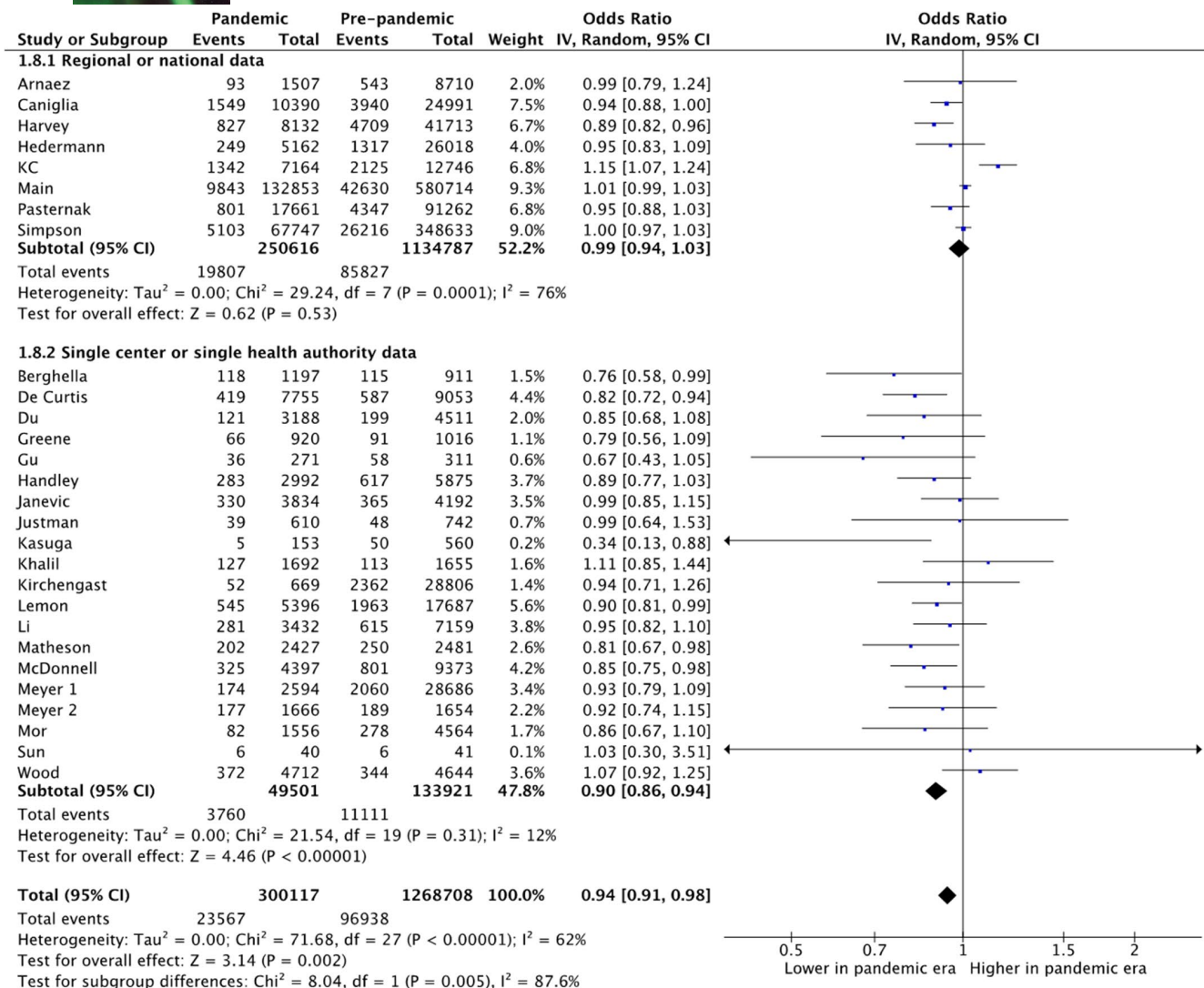


FIGURE 2 Forest plot for odds of preterm birth <37 weeks' gestation in pandemic vs pre-pandemic periods. CI, confidence interval, IV, inverse variance [Color figure can be viewed at wileyonlinelibrary.com]

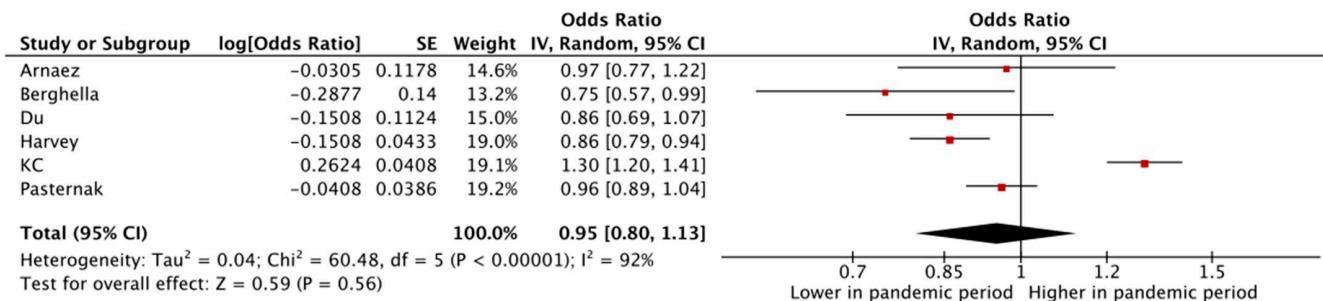


FIGURE 3 Forest plot for adjusted odds of preterm birth <37 weeks' gestation in pandemic vs pre-pandemic periods. CI, confidence interval, IV, inverse variance [Color figure can be viewed at wileyonlinelibrary.com]

across the included studies; however, the change in PTB rate between periods was not baseline-rate dependent. Although we did not observe any differences in subgroups of PTB using different gestational age cut-offs (ie <34, <32 and <28 weeks), not all studies contributed to these analyses.

Recently, Chmielewska et al.⁴⁹ reported results from a systematic review and meta-analyses including studies evaluating studies assessing population-level impact during pandemic period published up to 8 January 2021. They reported no difference in PTB rate (15 studies, uaOR 0.94, 95% CI 0.87–1.02) but an increase in stillbirth

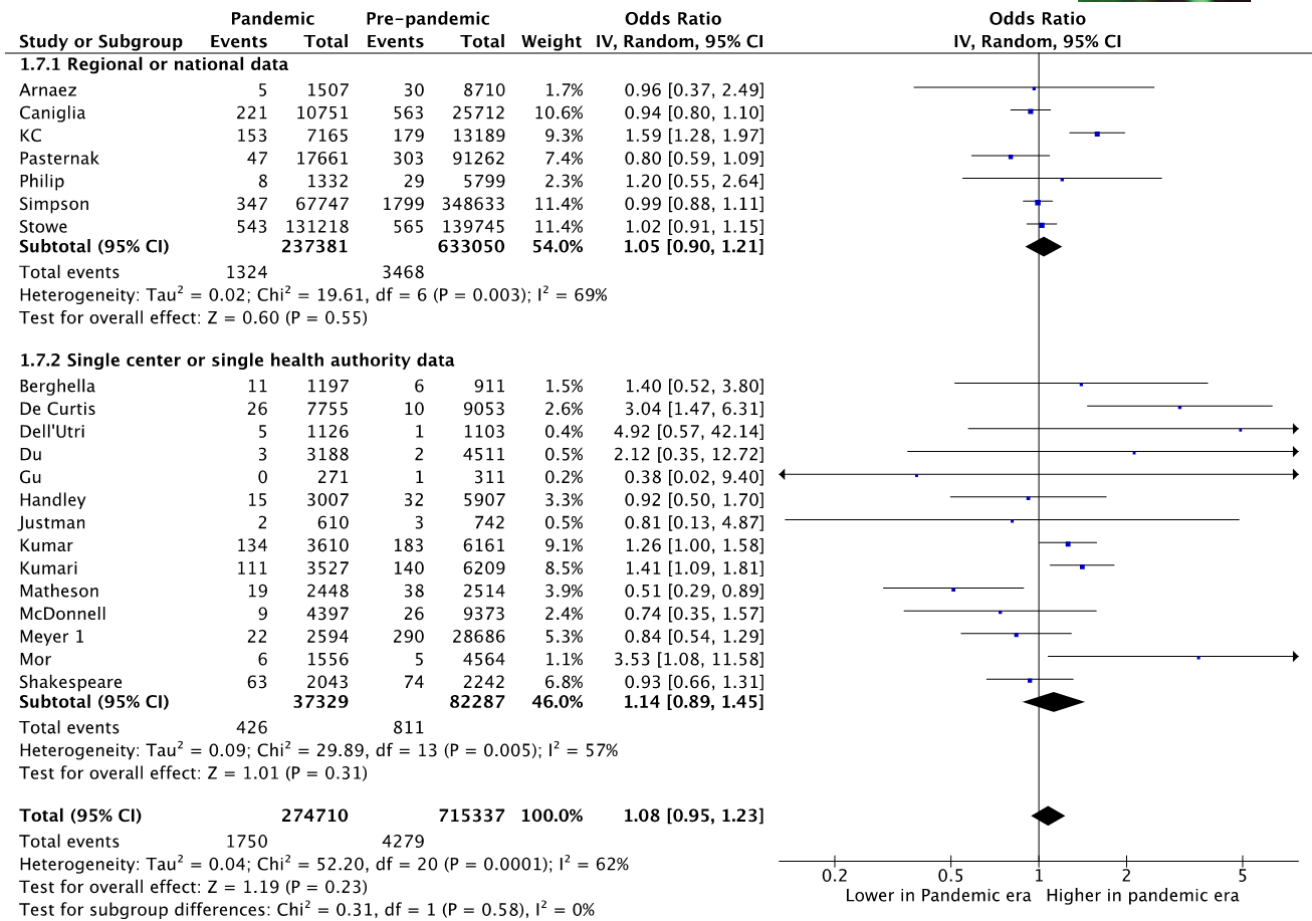


FIGURE 4 Forest plot for odds of stillbirth in pandemic vs pre-pandemic periods. CI, confidence interval, IV, inverse variance [Color figure can be viewed at wileyonlinelibrary.com]

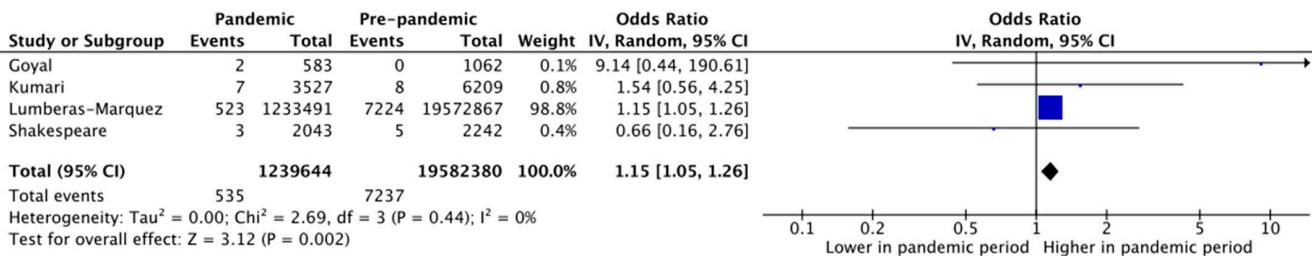


FIGURE 5 Forest plot for odds of maternal mortality in pandemic vs pre-pandemic periods. CI, confidence interval, IV, inverse variance [Color figure can be viewed at wileyonlinelibrary.com]

(12 studies, uaOR 1.28, 95% CI 1.07-1.54) and maternal mortality. With availability of data from 13 more studies on PTB and nine more studies for stillbirth, the results have remarkably changed, although this could also partly relate to minor differences in study inclusion criteria and data extraction. The larger number of subjects included in pooled analyses in our review has improved the precision of pooled estimates, thus increasing confidence in the findings, particularly for less common secondary outcomes; nonetheless, this is the main reason for conducting this as a living systematic review so the information can be updated regularly.

The effects of lockdowns and mitigation strategies had contrasting effects in high- vs low- and middle-income countries.⁴⁹ Reports

from low-resource settings described increased fear and stress among pregnant individuals, reluctance to access in-hospital care during a pandemic, financial or employment issues, childcare or home schooling challenges, maternity staff shortages, reduced access to in-hospital care, and perceived or actual reductions in available obstetric services, resulting in a significant reduction in institutional births.^{8,9,17,30,31} Some reports noted a reduction in PTB and attributed this to a number of social and health behaviors associated with the pandemic,^{2,7} including decreased physical and mental stress due to better work-life balance,^{6,16,37} better support systems and financial assistance,^{16,28} improved nutrition, better hygiene,^{8,12} reduced physical activity,^{6,16,28,33} reduced exposure to infection,^{8,16,37,50} lower incidence of smoking and

Outcome	No. of studies	Pandemic period (n/N)	Pre-pandemic period (n/N)	OR (95% CI)	I ² (%)
PTB <34 weeks	8	523/21 240	1592/62 282	0.87 (0.70–1.07)	67
PTB <32 weeks	13	3668/263 626	14 366/ 1 198 164	0.96 (0.78–1.19)	94
PTB <28 weeks	10	1136/240 218	5404/1 085 624	0.92 (0.79–1.06)	51
Spontaneous PTB	5	767/16 724	1685/31 598	0.89 (0.82–0.98)	0
Induced PTB	4	583/12 012	1453/26 954	0.90 (0.81–1.00)	0
Low birthweight	7	1673/24 121	7194/99 667	0.90 (0.80–1.02)	53
Very low birthweight	5	205/15 292	1366/114 636	1.03 (0.71–1.49)	65
Extremely low birthweight	4	33/7167	299/73 001	0.83 (0.32–2.17)	72
Neonatal mortality	6	583/90 976	1263/419 057	1.34 (0.71–2.55)	96
Birthweight, g	6	13 871 ^a	49 152 ^a	17.0 (6.9–27.6) ^b	0

TABLE 3 Results of studies reporting other outcomes

PTB, preterm birth.

^aBirthweight is shown as total number.

^bValue shown is mean difference (95% CI) in grams.

drug use due to reduced access and being indoors,¹⁶ lower pollution exposure and levels in environment,^{16,51} and fewer medical interventions secondary to reduced antenatal surveillance.^{7,16,37,45} The differences in PTB findings between single-center/adjacent hospitals studies and national/regional studies could reflect a change in referral patterns due to reduced access or the fact that pregnant individuals opted to give birth in hospitals with lower prevalence of COVID-19 or in non-COVID-designated hospitals.²⁷ Future studies are needed to explore these differences.

Although we did not observe an overall change in the odds of stillbirth during the pandemic period, several individual studies, mostly single-center in scope, reported increased odds of stillbirth compared to pre-pandemic time periods. The increase in stillbirth reported by these studies was attributed to reduced antenatal surveillance, a reluctance to access in-hospital care due to increased stress and anxiety^{9,18,30,33,39} or missed appointments due to rapid changes in maternity services during the pandemic.⁵⁰ These reasons may also explain an increase in maternal mortality identified in Mexico³⁴; however, according to those authors, the data from a government website were preliminary in scope and may change as more data become available. This could be a signal to be vigilant in attending the mother–fetus dyad during difficult public health emergency situations.

We did not find any significant differences between the pandemic and pre-pandemic periods for other outcomes, except for a marginal difference in birthweight. Since these data came from only five studies, further studies are needed to clarify this association, as a difference of 17 g is unlikely to be of clinical significance. Other factors that could be responsible for the differences between study findings include variations in the etiology of adverse pregnancy outcomes in different countries,^{2,17} initiatives by local governments to provide support to those at risk for higher stress,⁷ and changes to national legislation on pregnancy termination during the study period potentially influencing the incidences of stillbirth and PTB.^{2,7}

A key strength of our review was the inclusion of large populations from 18 countries, mainly arising from national or state or provincial data. Most included studies came from registries or similar types of datasets. In addition, we only included studies that reported on temporal changes in outcomes in the overall population, not data specifically from women affected by COVID-19. However, our study has limitations. There may be other relevant studies that are not yet published (and thus are not included), as the pandemic is still ongoing and many countries are facing a second or third wave of infections and associated public health restrictions. There was clinical and methodologic heterogeneity across studies regarding pandemic and pre-pandemic period definitions, population bases (single-center/adjacent hospitals vs regional/national) and choices of statistical methodologies. To overcome these limitations, we planned a priori to include pre-pandemic duration in meta-regression analyses, and we conducted post-hoc subgroup analyses on the type of studies. We were able to explain statistical heterogeneity to an extent for both of our primary outcomes. Some studies included the entire population of pregnant women, comprising those who did and did not have COVID-19 infection in their sample. When studies that categorically excluded women with COVID-19 infection were included in our review, we identified no difference in PTB or stillbirth. Finally, there were an insufficient number of studies to assess some of the prespecified outcomes, including maternal mortality.

The COVID-19 pandemic has affected many countries with very high case numbers, such as India, Brazil, the UK and Italy, yet large, population-based estimates on pregnancy outcomes from these countries were lacking in this review. National registries from these and other countries would be ideally suited to investigate the impact of the pandemic on perinatal health at a population level. A harmonization of methodological approaches would also facilitate the assessment of the effects of the pandemic period on fetal, neonatal and maternal outcomes, as high methodological heterogeneity makes direct comparisons challenging. One important point to consider

going forward will be that the rates of these outcomes fluctuate with natural variation over time. We hope to capture these fluctuations through 3-monthly updates of this living systematic review. Future investigations should use approaches that can elucidate whether any fluctuation observed in a particular setting during the pandemic period is outside the range of expected natural variation.

5 | CONCLUSION

In pooled analyses, we observed reductions in the unadjusted odds of PTB between the pandemic and pre-pandemic periods; especially spontaneous PTB. However, this finding was driven by single-center studies. There was no difference in analyses of adjusted estimates of PTB or within subgroups of PTB. Although we did not observe meaningful differences in other outcomes, including odds of stillbirth, the data were more limited and precluded a robust assessment. Higher maternal mortality reported from Mexico indicates that further studies from low- and middle-income regions highly affected by COVID-19 are needed where drastic changes in the healthcare access, healthcare availability, and personal, social and environmental factors contributed disproportionately to adverse pregnancy outcomes. Since the findings are changed between reviews published recently and current reviews, there is a need for a living systematic review which can be updated regularly.

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AUTHOR CONTRIBUTIONS

PSS conceptualized and designed the study and conducted and executed the search strategy. PSS and JY screened study titles, abstracts, and full texts; completed the analysis and risk of bias assessments; and wrote the first draft of the manuscript. AK, DBF, JWS, KEM, and RD contributed to the data interpretation, commented on all versions of the manuscript, and approved the final draft. All authors have approved this version of the manuscript as submitted, and all agree to be accountable for its accuracy.

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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